Integrated Science Assessment for Carbon Monoxide –
First External Review Draft

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 (varies between 0 and 1)
a	air exchange rate of the microenvironment
AA	abdominal aorta(s)
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 - protein family (of protein kinases B [PKB[)
AM, a.m.	morning hours
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANOVA	analysis of variance
APO E	apolipoprotein E
APO E$^{-/-}$	mouse strain used as a model of atherosclerosis
ARI	acute respiratory infection
AP	action potential
APD	action potential duration
APEX	Air Pollution Exposure (population-based model)
APHEA	Air Pollution and Health: A European Approach (multi-cities analyses)
APHEA2	extended analysis of APHEA
APTT	activated partial thromboplastin time, (blood coagulability endpoint)
AQ	air quality
AQCD	Air Quality Criteria Document
AQS	(EPA) Air Quality System (database)
AR	gastronomy reared with artificial feeding system (milk substitutes using gastronomy-feeding)
ARCO	gastronomy reared + CO exposure
ARIC	Atherosclerosis Risk in Communities (study)
ARID	gastronomy reared with iron deficient diet
ARIDCO	gastronomy reared with iron deficient diet + CO exposure
ATP	adenosine triphosphate
ATS	American Thoracic Society
avg	average
AVP	aortic valve prosthesis (surgically implantable biological 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	a selective endothelin A (ET_A) receptor antagonist
BS	black smoke
BSP	black smoke particles
C	carbon
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
CALPUFF	Gaussian puff modeling system to simulate air quality dispersion and accesses long range transport of pollutants. Distributed by TRC Solutions.
CAMP	Childhood Asthma Management Program (study)
cAMP	cyclic AMP
CAP(s)	compound action potential(s)
CASAC	Clean Air Scientific Advisory Committee
CASN	Cooperative Air Sampling Network
CAth	cardiac atherosclerosis
CBSA	Core-Based Statistical Area (containing at least one urban area of 10,000 people [as determined by the 2000 census]; replaces the older MSA definition from the 1990 census).
CCGG	Carbon Cycle Greenhouse Gases Group (within ESRL)
CD	cardiac dysrhthmias
Cd	cadmium
CD-1	mouse strain
CDC	Centers for Disease Control and Prevention
$CdCl_2$	cadmium chloride
CFK	Coburn-Forster-Kane (equation or modeling)
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 (a measurement of visibility interference in the atmosphere, as the quantity of dust and smoke in a theoretical 1,000 linear feet of air).
COHb	carboxyhemoglobin (% concentration measured in (mL CO/mL blood))
$[COHb]_0$	carboxyhemoglobin concentration at time zero (0)
$[COHb]_t$	carboxyhemoglobin concentration at time t
COMb	carboxymyoglobin
Complex IV	mitochondrial cytochrome c oxidase complex assembly, respiratory chain complex IV in the mitochondrial inner membrane.
Cong	U.S. Congress
CONUS	contiguous U.S. (United States of America)
COPD	chronic obstructive pulmonary disease
CPS II	Cancer Prevention Study II
C-R	concentration-response (relationship)
CRC	Coordinating Research Council
CrMP	collapsin response mediator protein
CRP	C-reactive protein
CSA	Combined Statistical Area (an aggregate of adjacent CBSAs tied by specific commuting behaviors), as defined by the 2000 census
Cu	copper (element)
CVD	cardiovascular disease
Δ	delta, change, difference
d	straight-line distance between monitor pairs
Dahl/Rapp	salt-sensitive model of hypertension (substrain of Sprague Dawley rat)
D.C.	District of Columbia

df	degrees of freedom
df/yr	degrees of freedom per year
D_L	lung diffusing capacity
D_LCO	lung diffusing capacity of CO (in mL/min/mmHg)
D_mCO	capacity for diffusion of CO into the muscle
DMT-1	divalent metal transporter-1 protein (transport and detoxification of metals)
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
dt	time spent in each location
Σ	sigma, sum of a series
E	exposure over some duration
E_a	exposure to pollutant of ambient origin
E/A	mitral ratio of peak early to late diastolic filling velocity (E/A).
EC	elemental carbon
ED	emergency department
EKG, ECG	electrocardiogram; electrical activity of the heart over time, measured by an electrocardiograph
E_{na}	exposure to pollutant of non-ambient origin
eNOS	endothelial nitric oxide synthase
EPA	U.S. Environmental Protection Agency
EPO	erythropoietin (stimulates production of new red blood cells)
EPR	Electron Paramagnetic Resonance (spectroscopy), aka Electron Spin Resonance (spectroscopy)
EPRI	Electric Power Research Institute
ERK1/2	ERK-1 (MAPK p42) and ERK-2 (MAPK p44) (extracellular signal-regulated kinases [in cell signaling pathway])
ESRL	Earth System Research Laboratory (within GMD of NOAA)
ET-1	endothelin-1; vasoconstrictor that mediates regulation of vascular tone
ET_A	endothelin A (ET_A) receptor subtype
ETS	environmental tobacco smoke
EXPOLIS	six-city European air pollution study
Factor VII	FVII, a vitamin K-dependent serine protease glycoprotein (also known as stable factor or proconvertin), initiates the process of coagulation.
Factor VIIIC	blood-coagulation factor VIII. (antihemophilic factor, part of factor VIII/von Willebrand factor complex; acts in the intrinsic pathway of blood coagulation
FAS	apoptosis stimulating fragment
FC	interference filter
Fe	iron

Fe^{2+}	ferrous iron
Fe^{3+}	ferric iron
FEF	forced expiratory flow (Liters/second)
FEF_{25-75}	determined from the time in seconds at which 25% and 75% of the vital capacity is reached. The volume of air exhaled between these two times is the FEF_{25-75}. This value reflects the status of medium and small sized airways.
FEM	Federal equivalent method
FEV_1	forced expiratory volume in 1 second (volume of air exhaled into the spirometer mouthpiece in one second, using maximum effort)
f_i	fraction of time spent indoors
F_ICO	fractional concentration of CO in ambient air (in ppm)
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 (volume of air that is expelled into the spirometer following a maximum inhalation effort)
FVII	Factor VII, a vitamin K-dependent serine protease glycoprotein (also known as stable factor or proconvertin), initiates the process of coagulation
FW	fresh weight
G0/G1 phase	Phase of Cell Cycle in which cell commits to mitosis (division)
g, mg, μg	gram(s), milligram(s), microgram(s)
g/mole	unit of molar mass (grams/mole)
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 (of NOAA)
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_2	molecular hydrogen

H_2O	water
H_2O_2	hydrogen peroxide
H9c2	rat embryonic cardiomyocytes (cell line)
Hb	hemoglobin
HC(s)	hydrocarbon(s)
HCFC(s)	hydrochlorofluorocarbon(s)
HCO	formyl radical
HEAPSS	Health Effects of Air Pollution among Susceptible Subpopulations (study)
hectoPascal	atmospheric level measured by atmospheric pressure (e.g., 700 hectoPascals $\approx$10,000 feet above sea level)
HEK293	human embryonic kidney cells (experimentally transformed cell line)
Hem	hemorrhagic (stroke)
Hep3B	Human hepatocarcinoma cell line
HF	heart failure
HF	high energy frequency (HRV parameter)
HFLFR	high energy frequency versus low energy frequency ratio (HRV parameter)
HH	hypobaric hypoxia (measured in torr)
HIF-1α	oxygen-responsive component of the hypoxia-inducible factor (HIF) 1 complex
his-Fe^{2+}-his	iron binding scheme in neuroglobin (Nb); hexacoordinated deoxy ferrous (Fe^{2+}) form of Nb, bound to histidine
HO	heme oxygenase (microsomal enzyme that degrades heme protein to form endogenous CO and iron (Fe^{2+}))
HO_2	hydroperoxy radical, hydrogen dioxide
HO-1	inducible isoform of heme oxygenase (induced by stressors)
HO-2	constitutively expressed isoform of heme-oxygenase
HO/CO	heme oxygenase/carbon monoxide system (signaling pathway)
HR	heart rate (beats per minute), hazard ratio
H/R	hypoxia followed by reoxygenation
HRV	heart rate variability (beat-to-beat alterations in the heart determined by analyses of time and frequency domains in ECG(s).
HUVEC(s)	human umbilical vein endothelial cell(s)
hν	photon
H/W	height to width ratio
I	electrical current
IARC	International Agency for Research on Cancer
IC	inferior colliculus (an auditory integrative section of the midbrain)
$I_{ca,L}$	electrical current (I) through the L-type Ca^{2+} channel
ICAM-1	intercellular adhesion molecule
ICD	implantable cardioverter defibrillator(s)
ICR	substrain of CD1 mouse, Institute for Cancer Research
IDW	inverse-distance-weighted
IHD	ischemic heart disease

IL-6	interleukin-6
IL-8	interleukin-8
INDAIR	Indoor Air Model
I/O	indoor to outdoor concentration ratio
IOM	Institute of Medicine
i.p.	intraperitoneal injection
IQR	interquartile range
IR	immunoreactivity
IS	ischemic stroke
ISA	Integrated Science Assessment
Isch	ischemic (stroke)
ITA	internal thoracic artery of the heart (coronary artery bypass surgery graft)
I_{to}	transient outward current
i.v.	intravenous (injection)
IUGR	intrauterine growth restriction
K^+	potassium ion
k	dissociation rate, rate of CO loss from the microenvironment
k_{CO}	dissociation rate of carbon monoxide from hemoglobin
kHz	kilohertz (1,000 cycles per second; frequency of an electrical signal)
K_m	Michaelis Constant; the substrate concentration which gives $\frac{1}{2}$ V_{max} (in the Michaelis-Menten equation of enzyme kinetics)
km	kilometer(s)
K_m/V_{max}	slope of Michaelis-Menten equation; measures the efficency of an enzyme
k_{O2}	Dissociation rate of oxygen from hemoglobin
L, dL, mL, µL	Liter, deciLiter, milliLiter, microLiter
lag 0	same day as the hospital, ED, clinic, physician visit
lag 0-3	the three previous days before the hospital, ED, clinic, physician visit
LBW	low birth weight (<2,500 grams, (≈5lbs, 8 oz))
LCA+	leucocyte common antigen cells
LD	lactational day
LDH	lactate dehydrogenase (release of LDH is an indicator of cell membrane damage)
LDL	low-density lipoprotein
leeward	downwind
LF	low energy frequency (HRV parameter)
LF/HF	low energy frequency to high energy frequency ratio (HRV parameter)
LH	luetenizing hormone
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOESS	locally weighted scatterplot smoothing (modeling method); aka LOWESS
LPS	lipopolysaccharide
LTP	long-term potentiation (hippocampal)

LUR	land use regression (model[s])
LV	left ventricle (of heart)
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, cm, μm, nm	meter(s), centimeter, micrometer(s) = micron(s), nanometer(s)
M, mM, μM, nM, pM	Molar, milliMolar, microMolar, nanoMolar, picoMolar
M	Haldane coefficient representing the CO chemical affinity for Hb [or Mb]), Reaction mediator.
ma	moving average
MAPK	mitogen-activated protein kinase(s), MAP kinase(s)
MAO-A	monoamine oxidase A (mitochondrial enzyme; deaminates amine-neurotransmitters)
max	maximum
Mb	myoglobin
MC	ultrafine particle mass concentration
METs	metabolic equivalent unit(s)
mg/m^3	unit of chemical concentration in air (milligrams per cubic meter)
MHC	major histocompatibility complex
MI	myocardial infarction, "heart attack"
Miller PEE	Miller equation prediction equation estimates
min	minute(s)
MIP-2	macrophage inflammatory protein-2
mitral E to A ratio	mitral ratio of peak early to late diastolic filling velocity (E/A).
MMEF	maximal midexpiratory flow
mmHg	millimeters of mercury (unit of pressure)
MMP	matrix metalloproteinase
MOA(s)	mode(s) of Action
MOBILE6	(EPA) Mobile source emission factor model
MODIS	Moderate Resolution Imaging Spectroradiometer
mol, nmol	mole, nanomole
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease (study)
MOPITT	Measurement of Pollution in the Troposphere (instrument)
MPO	myeloperoxidase (indicative of neutrophil degranulation)
MPT	mitochondrial permeability transition
MR	maternally reared; rodent pups reared with their respective dams
mRNA	messenger RNA
ms	millisecond(s)
MSA	Metropolitan Statistical Area
MSNA	muscle sympathetic nerve activity

MT	million tons
MV_{O2}	myocardial oxygen consumption
n, N	sample size
N	number of monitor days
N_2	nitrogen gas
NAAQS	National Ambient Air Quality Standards
NADPH	nicotinamide adenine dinucleotide phosphate
NADH-TR	nicotinamide adenine dinucleotide - tetrazolium reductase; histochemical stain of muscle tissue - the space between the myofibrils.
NAPAP	National Acid Precipitation Assessment Program
NARSTO	(formerly) 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 (detection)
NE	norepinephrine
NEI	(EPA) National Emissions Inventory
NF-κB	nuclear factor kappa B
Ni	nickel (element)
NIHL	noise-induced hearing loss
NMDA	N-methyl-D-aspartate
NMHC(s)	nonmethane hydrocarbon(s)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
nmol	nanomole
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 radicals, free radical species of nitric oxide
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_2	oxygen
O_3	ozone
O_2Hb	oxyhemoglobin (% concentration in mL O_2 / mL blood)
O_2Mb	oxymyoglobin

OAE	otoacoustic emissions (testing)
OAQPS	Office of Air Quality Planning and Standards
OC	organic carbon
OH, OH OH$^\bullet$	hydroxyl group, hydroxyl radical(s)
OR	odds ratio(s)
OS	occlusive stroke
OSPM	Operational Street Pollution Model
P	penetration (of pollutant)
P, p	probability
P	number of paired hourly observations
P_1CO	CO partial pressure in inhaled air (in mmHg)
P13K	phosphoinositide 3-kinase
p21$^{Waf1/Cip1}$	inhibitor of CDK(s) (cyclin-dependent kinases) - regulates cell cycle arrest following DNA damage.
p38	p38 MAP kinase
P90	90th percentile of the absolute difference in concentrations
P450	cytochrome P450
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; (involved in DNA repair; cleaved by caspases during early apoptosis)
Pb	lead
PB	barometric pressure (in mmHg)
PBN	the free radical inhibitors PBN (a spin trap) or N-tert-butyl-alpha-phenylnitrone (free radical inhibitor) an organic spin trap agent designed specifically to form "stable" adducts with free radicals in electron spin resonance studies.
$P_{\bar{C}}$	average partial pressure in lung capillaries
pCO	partial pressure of CO in lung capillaries (in mmHg)
P_{CO}	partial pressure of CO
$P_{\bar{C}}O_2$	average partial pressure of O_2 in lung capillaries (mmHg)
PDGF	platelet derived growth factor
PEE	prediction equation estimates
PEF	peak expiratory flow (L/min)
PEFD(s)	Personal Exposures Frequency Distributions

PEM(s)	personal exposure monitor(s)
%	percent
PHD	pulmonary heart disease
P_I	partial pressure of inhaled air
Pi	inorganic phosphate
PIH	primary intracerebral hemorrhage
PKB	protein kinases B
PM	particulate matter
p.m.	afternoon/evening hours
$PM_{2.5}$	fine particulate matter, particles with a nominal mean aerodynamic diameter less than or equal to 2.5 μm
PM_{10}	particles with a mean aerodynamic diameter less than or equal to 10 μm
$PM_{10-2.5}$	coarse particulate matter, coarse fraction of PM_{10} (referred to as thoracic coarse particles or coarse-fraction particles; generally including particles with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm).
PMN	polymorphonuclear leukocytes
pmol	picomole
PNC	particle number concentration / count
PND	post natal day
pNEM/CO	probabilistic NAAQS Exposure Model for CO (preceded APEX)
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 (in mmHg)
ppb	parts per billion
ppm	parts per million
PRB	policy-relevant background
PT	prothrombin time (blood coagulability endpoint)
PTB	preterm birth (birth after the 20th week, but before the 38th week of human pregnancy)
PVCD	peripheral vascular and cerebrovascular disease
PvO_2	venous oxygen tension
PVO_2	peak oxygen consumption
$\dot{Q}$	cardiac output
QCP	Quantitative Circulatory Physiology (model)
$\dot{Q}_M$	blood flow to muscle
$\dot{Q}_{OT}$	blood flow to other tissues
r	correlation coefficient
R^2	coefficient of determination
R State	R state of hemoglobin; structural shape of protein when binding oxygen (oxy state)
RA	radial artery of the heart
RAW 264.7	mouse macrophage cell line

RBC	red blood cell
redox status	ratio of interconvertible reduced/oxidized forms of a molecule
rho(0)	rho(0) cells (cells lacking mitochondrial DNA)
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 (study)
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
S	second(s)
SA	sphinganine
SAA	serum amyloid A
SAB	(EPA) Science Advisory Board
SBP	systolic blood pressure
SDNN	standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
Se	selenium
SEM	standard error of mean
sEng	soluble endoglin
SES	socioeconomic status
Sess	Session (of Congress)
SF_6	sulfur hexafluoride (tracer gas)
sFlt	soluble Fms-like tyrosine kinase-1
SGA	small for gestational age
sGC	soluble guanylate cyclase
SHEDS	(EPA) Stochastic Human Exposure and Dose Simulation (model)
SHR	Spontaneously hypertensive rat strain
SIDS	sudden infant death syndrome
SIPs	State Implementation Plan(s)
siRNA	small inhibitory RNA (silencing RNA)
SLAMS	State and Local Air Monitoring Stations
SMC	smooth muscle cell(s)
Sn	tin

snMP	tin-(IV)-mesoporphyrin (HO inhibitor)
SNP	single-nucleotide polymorphism
SnPP-IX	tin protoporphyrin IX, (HO inhibitor)
SO	sphingosine
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SOD	superoxide dismutase
SOD1	cytoplasmic superoxide dismutase
SOD2	mitochondrial superoxide dismutase
SOPHIA	Study of Particles and Health in Atlanta
ST-segment	segment of EKG between QRS complex, and T wave. ST-segment elevation may indicate myocardial infarction
STAT1 / STAT3	signal transducers and activators of transcription (transcription factors involved in cell signaling)
STEMS	Space-Time Exposure Modeling System
STN	(EPA) Speciation Trends Network
STPD	standard temperature and pressure, dry
SV	stroke volume
SVEB	supraventricular (atrium or atrioventricular node) ectopic beats
τ	photochemical lifetime
T	trial
T lymphocytes	thymus-dependent lymphocytes
T State	T state of hemoglobin; structural shape of protein when not binding oxygen (deoxy state)
TBARS	thiobarbituric acid reactive substances
TC	total carbon
TFAM	mitochondrial transcription factor A
Tg	teragram(s)
TH	tyrosine hydroxylase
TH_b	total blood concentration of hemoglobin (in g Hb/mL blood)
THP-1	human monocyte-derived cell line, (can differentiate into macrophages)
TIA	transient ischemic attack (mini-stroke)
TNF-α	tissue necrosis factor alpha (WBC protein boosts immune system, too much can cause inflammation)
torr	unit of pressure, equal to 0.001316 (1/760) atmosphere
TPM	total particulate matter
TSP	total suspended particles
UFP	ultrafine particle(s)
U.K.	United Kingdom
ULTRA	(Exposure and Risk Assessment for Fine and)Ultrafine Particles in Ambeint Air (Study)
URI	upper respiratory infection
U.S.	United States of America
USC	U.S. Code

UV	ultraviolet
V	vanadium
$\dot{V}$	minute ventilation
$\dot{V}_A$	alveolar ventilation (in mL/min at STPD)
V_A	alveolar volume, a mesuremnt of lung size
V_b	blood volume (in mL)
$\dot{V}_{CO}$	CO uptake rate (the product of D_LCO and the mean P_ACO).
$\dot{V}_{CO}$	endogenous CO production rate (in mL/min at STPD)
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 (catalyzed by a fixed enzyme concentration, in the Michaelis-Menten equation of enzyme kinetics)
VO_2 max	maximum volume per time, of oxygen (maximal oxygen consumption, maximal oxygen uptake or aerobic capacity)
VOC(s)	volatile organic compound(s)
vol	volume
VPB	ventricular premature beat
V/Q	ventilation-perfusion ratio
vWF	von Willebrand factor (part of factor VIII/von Willebrand factor complex; acts in the intrinsic pathway of blood coagulation)
W	width
WBC	white blood cell
WHI	Women's Health Initiative (Study)
windward	upwind
WKY	Wistar-Kyoto rat strain
ww	wet weight
X_{ij}, X_{ik}	observed hourly concentrations for time period i at sites j and k
yr	year
Z/H	elevation of the measurement (Z) scaled by height (H)
ZIP (code)	Zone Improvement Plan (system of postal codes used in the U.S.)
Zn	zinc
ZnPP IX	Zn protoporphyrin IX, HO inhibitor

Chapter 1. Introduction

1   The Integrated Science Assessment (ISA) is a concise evaluation and synthesis of the most policy-

2   relevant science for reviewing the national ambient air quality standards (NAAQS). Because the ISA

3   communicates critical science judgments relevant to the NAAQS review, it forms the scientific

4   foundation for the review of the NAAQS for carbon monoxide (CO). The existing primary CO standards

5   include a 1-hour (h) average (avg) standard set at 35 parts per million (ppm), and an 8-h avg standard set

6   at 9 ppm, neither to be exceeded more than once per year. There is currently no secondary standard for

7   CO.

8   The ISA accurately reflects "the latest scientific knowledge useful in indicating the kind and extent

9   of identifiable effects on public health which may be expected from the presence of [a] pollutant in

10   ambient air" (U.S. Code, 1970). Key information and judgments formerly contained in the Air Quality

11   Criteria Document (AQCD) for CO are incorporated in this assessment. Additional details of the pertinent

12   scientific literature published since the last review, as well as selected older studies of particular interest,

13   are included in a series of annexes. This first external draft ISA thus serves to update and revise the

14   information available at the time of the previous AQCD for CO in 2000.

15   The Integrated Plan for Review of the NAAQS for CO (U.S. EPA, 2008b) identifies key policy-

16   relevant questions that provide a framework for this review of the scientific evidence. These questions

17   frame the entire review of the NAAQS and thus are informed by both science and policy considerations.

18   The ISA organizes and presents the scientific evidence such that it, when considered along with findings

19   from risk analyses and policy considerations, will help the U.S. Environmental Protection Agency (EPA)

20   address these questions during the NAAQS review:

21   ▪   Has new information altered the scientific support for the occurrence of health effects

22   following short- and/or long-term exposure to levels of CO found in the ambient air?

23   ▪   To what extent is key evidence becoming available that could inform our understanding of

24   human subpopulations that are particularly sensitive to CO exposures? Is there new or

25   emerging evidence on health effects beyond cardiovascular and respiratory endpoints

26   (e.g., systemic effects, developmental effects, birth outcomes) that suggest additional

27   sensitive subpopulations should be given increased focus in this review (e.g., neonates)?

28   ▪   What do recent studies focused on the near-roadway environment, including bus stops and

29   intersections, tell us about high-exposure human subpopulations and the health effects of CO?

30   What information is available on elevated exposures due to other transportation sources, such

1   as shipping, port operations, and recreational vehicles? What is the effect of altitude on CO

2   sources and health effects?

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

4   ▪   To what extent is key scientific evidence becoming available to improve our understanding of

5   the health effects associated with various time periods of CO exposures, including not only

6   daily, but also chronic (months to years) exposures? To what extent is critical research

7   becoming available that could improve our understanding of the relationship between various

8   health endpoints and different lag periods (e.g., single day, multi-day distributed lags)?

9   ▪   To what extent does the evidence suggest that alternate dose indicators other than

10   carboxyhemoglobin (COHb) levels (e.g., tissue oxygenation) should be evaluated to

11   characterize the biological effect?

12   ▪   Has new information altered conclusions from previous reviews regarding the plausibility of

13   adverse health effects caused by CO exposure?

14   ▪   To what extent have important uncertainties identified in the last review been reduced and/or

15   have new uncertainties emerged?

16   ▪   Have new information or scientific insights altered the scientific conclusions regarding the

17   occurrence of direct (or indirect) welfare effects associated with levels of CO found in the

18   ambient air?

1.1. Legislative Requirements

19   Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS.

20   Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list "air pollutants" that "in [her]

21   judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence …

22   in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality

23   criteria for those that are listed (42 U.S.C. 7408). Air quality criteria are intended to "accurately reflect the

24   latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health

25   or welfare which may be expected from the presence of [a] pollutant in ambient air…" 42 U.S.C. 7408(b).

26   Section 109 (42 U.S.C. 7409) of the Clean Air Act directs the EPA Administrator to propose and

27   promulgate "primary" and "secondary" National Ambient Air Quality Standards (NAAQS) for pollutants

28   listed under section 108. Section 109(b)(1) defines a primary standard as one "the attainment and

29   maintenance of which in the judgment of the Administrator, based on such criteria and allowing an

1   adequate margin of safety, are requisite to protect the public health."[1] A secondary standard, as defined in

2   section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the

3   judgment of the U.S. EPA Administrator, based on such criteria, is required to protect the public welfare

4   from any known or anticipated adverse effects associated with the presence of [the] pollutant in the

5   ambient air."[2] The requirement that primary standards include an adequate margin of safety was intended

6   to address uncertainties associated with inconclusive scientific and technical information available at the

7   time of standard setting. It was also intended to provide a reasonable degree of protection against hazards

8   that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C.

9   Cir 1980), cert. denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176,

10 1186 (D.C. Cir. 1981) cert. denied, 455 U.S. 1034 (1982). The aforementioned uncertainties are

11 components of the risk associated with pollution at levels below those at which human health effects can

12 be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an

13 adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been

14 demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk

15 of harm, even if the risk is not precisely identified as to nature or degree.

16   In selecting a margin of safety, the EPA considers such factors as the nature and severity of the

17 health effects involved, the size of sensitive population(s) at risk, and the kind and degree of the

18 uncertainties that must be addressed. The selection of any particular approach to providing an adequate

19 margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries*

20 *Association v. EPA*, supra, 647 F.2d at 1161-62.

21   In setting standards that are "requisite" to protect public health and welfare, as provided in Section

22 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for

23 these purposes. In so doing, EPA may not consider the costs of implementing the standards. See *Whitman*

24 *v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (D.C. Cir. 2001).

25   Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals

26 thereafter, the Administrator shall complete a thorough review of the criteria published under section 108

27 and the national ambient air quality standards…and shall make such revisions in such criteria and

28 standards and promulgate such new standards as may be appropriate…" Section 109(d)(2) requires that an

29 independent scientific review committee "shall complete a review of the criteria…and the national

30 primary and secondary ambient air quality standards…and shall recommend to the Administrator any

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[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."

1 new…standards and revisions of existing criteria and standards as may be appropriate…" Since the early
2 1980s, this independent review function has been performed by the Clean Air Scientific Advisory
3 Committee (CASAC) of EPA's Science Advisory Board (SAB).

1.2. History of the NAAQS for CO

4 On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO, under
5 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
6 than once per year (36 FR 8186). In 1979, EPA published the *Air Quality Criteria Document for Carbon*
7 *Monoxide* (U.S. EPA, 1979a), which updated the scientific criteria upon which the initial CO standards
8 were based. A Staff Paper (U.S. EPA, 1979b) was prepared and, along with the AQCD, served as the basis
9 for development of proposed rulemaking (45 FR 55066) published on August 18, 1980. Delays due to
10 uncertainties regarding the scientific basis for the final decision resulted in EPA announcing a second
11 public comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA
12 prepared an Addendum to the 1979 AQCD (U.S. EPA, 1984b) and an updated Staff Paper (U.S. EPA,
13 1984a). Following review by CASAC, EPA announced its final decision (50 FR 37484) not to revise the
14 existing primary standard and to revoke the secondary standard for CO on September 13, 1985, due to a
15 lack of evidence of direct effects on public welfare at ambient concentrations.
16 In 1987, EPA initiated action to revise the criteria for CO and released a revised AQCD for CASAC
17 and public review. In a "closure letter" (McClellan, 1991) sent to the Administrator, the CASAC
18 concluded that the AQCD (U.S. EPA, 2000) ". . . provides a scientifically balanced and defensible
19 summary of current knowledge of the effects of this pollutant and provides an adequate basis for the EPA
20 to make a decision as to the appropriate primary NAAQS for CO." A revised Staff Paper subsequently
21 was reviewed by CASAC and the public, and in a "closure letter" (McClellan, 1992) sent to the
22 Administrator, CASAC stated ". . . that a standard of the present form and with a numerical value similar
23 to that of the present standard would be supported by the present scientific data on health effects of
24 exposure to carbon monoxide." Based on the revised AQCD (U.S. EPA, 2000) and staff conclusions and
25 recommendations contained in the revised Staff Paper (U.S. EPA, 1992), the Administrator announced the
26 final decision (59 FR 38906) on August 1, 1994, that revision of the primary NAAQS for CO was not
27 appropriate at that time.
28 In 1997, revisions to the AQCD were initiated. A workshop was held in September 1998 to review
29 and discuss material contained in the revised AQCD. On June 9, 1999, CASAC held a public meeting to
30 review the draft AQCD and a draft exposure analysis methodology document. Comments from CASAC
31 and the public were considered in a second draft AQCD, which was reviewed at a CASAC meeting, held
32 on November 18, 1999. After revision of the second draft AQCD, the final AQCD (U.S. EPA, 2000) was

1   released in August 2000. EPA put the review on hold when Congress called on the National Research

2   Council (NRC) to conduct a review of the impact of meteorology and topography on ambient CO

3   concentrations in high altitude and extreme cold regions of the U.S. In response, the NRC convened the

4   committee on Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas, which

5   focused on Fairbanks, Alaska as a case study in an interim report, which was completed in 2002. A final

6   report, *Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem Are*as, was

7   published in 2003 (NRC, 2003) and offered a wide range of recommendations on management of CO air

8   pollution, cold start emissions standards, oxygenated fuels, and CO monitoring. EPA did not complete the

9   review which started in 1997.

1.3. Document Development

10   EPA initiated the current review of the NAAQS for CO on September 13, 2007 with a call for

11   information from the public (72 FR 52369). In addition to the call for information, publications were

12   identified through an ongoing literature search process that includes extensive computer database mining

13   on specific topics. Additional publications were identified by EPA scientists in a variety of disciplines by

14   combing through peer-reviewed scientific literature obtained through these ongoing literature searches,

15   reviewing previous EPA reports, and a review of reference lists from important publications. All relevant

16   epidemiologic, human clinical, and animal toxicological studies, including those related to exposure-

17   response relationships, mode(s) of action (MOA), or susceptible subpopulations published since the last

18   review were considered. Added to the body of research were EPA's analyses of air quality and emissions

19   data, studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to

20   exposure to CO. A literature search conducted on the ecological effects of ambient CO did not identify

21   any relevant information. Further information was acquired from consultation with scientific experts and

22   the public.

1.4. Document Organization

23   The ISA is composed of five chapters. This introductory chapter presents background information,

24   and provides an overview of EPA's framework for making causal judgments. Chapter 2 is an integrated

25   summary of key findings and conclusions regarding the source to dose paradigm, MOA, and important

26   health effects of CO, including cardiovascular, nervous system, perinatal/developmental, respiratory, and

27   mortality outcomes. Chapter 3 highlights key concepts and evidence relevant to understanding the

28   sources, ambient concentrations, atmospheric behavior, and exposure to ambient CO. Chapter 4 describes

1   the dosimetry and pharmacokinetics of CO, including formation and fate of carboxyhemoglobin (COHb).

2   Chapter 5 presents a discussion of the MOA of CO and evaluates and integrates epidemiologic, human

3   clinical, and animal toxicological information on the health effects of CO, including cardiovascular and

4   systemic effects, central nervous system (CNS) effects, birth outcomes and developmental effects,

5   respiratory effects, and mortality.

6   A series of annexes supplement this ISA. The annexes provide tables summarizing additional

7   details of the pertinent literature published since the last review, as well as selected older studies of

8   particular interest. These annexes contain information on:

9   ▪ atmospheric chemistry of CO, sampling and analytic methods for measurement of CO

10   concentrations, emissions, sources and human exposure to CO (Annex A)

11   ▪ studies on the dosimetry and pharmacokinetics of CO (Annex B)

12   ▪ epidemiologic studies of health effects from short- and long-term exposure to CO (Annex C)

13   ▪ controlled human exposure studies of health effects related to exposure to CO (Annex D);

14   and

15   ▪ toxicological studies of health effects in laboratory animals (Annex E)

16   Within the Annexes, detailed information about methods and results of health studies is

17   summarized in tabular format, and generally includes information about concentrations of CO and

18   averaging times, study methods employed, results and comments, and quantitative results for

19   relationships between effects and exposure to CO.

1.5. Document Scope

20   For the current review of the primary CO standards, relevant scientific information on human

21   exposures and health effects associated with exposure to ambient CO has been assessed. Health effects

22   resulting from accidental exposures to very high concentrations of non-ambient CO (i.e., carbon

23   monoxide poisoning) are not directly relevant to ambient exposures, and as such, a discussion of these

24   effects has deliberately been excluded from this document. For a detailed review of the effects of high

25   level exposures to CO, the reader is referred to the extensive body of literature related to carbon

26   monoxide poisoning (Ernst and Zibrak, 1998; Penney, 2007; Raub et al., 2000). The possible influence of

27   other atmospheric pollutants on the interpretation of the role of CO in health effects studies is considered.

28   This includes other pollutants with the potential to co-occur in the environment (e.g., nitrogen dioxide

29   [NO_2], sulfur dioxide [SO_2], ozone [O_3], and particulate matter [PM]). The review also assesses relevant

30   scientific information associated with known or anticipated public welfare effects that may be identified.

1   As discussed in Section 1.3, a literature review of the ecological effects of ambient CO identified no
2   relevant information, and thus these effects are not assessed. With regard to climate effects this review
3   includes updates and additional data available since the 2000 CO AQCD on the interaction of largely
4   urban CO emissions and hydroxyl radical concentrations, and on background concentrations in the U.S.

1.6.   EPA Framework for Causal Determination

5   The EPA has developed a consistent and transparent basis to evaluate the causal nature of air
6   pollution-induced health or environmental effects. The framework described below establishes uniform
7   language concerning causality and brings more specificity to the findings. This standardized language was
8   drawn from across the federal government and wider scientific community, especially from the recent
9   National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive*
10   *Disability Decision-Making Process for Veterans* (IOM, 2008), the most recent comprehensive work on
11   evaluating causality.
12   This introductory section focuses on the evaluation of health effects evidence. While focusing on
13   human health outcomes, the concepts are also generally relevant to causality determination for welfare
14   effects. This section:

15   ▪   describes the kinds of scientific evidence used in establishing a general causal relationship
16   between exposure and health effects;

17   ▪   defines cause, in contrast to statistical association;

18   ▪   discusses the sources of evidence necessary to reach a conclusion about the existence of a
19   causal relationship;

20   ▪   highlights the issue of multifactorial causation;

21   ▪   identifies issues and approaches related to uncertainty; and

22   ▪   provides a framework for classifying and characterizing the weight of evidence in support of
23   a general causal relationship.

24   Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, human
25   clinical, and animal toxicological studies) have been formulated by a number of regulatory and science
26   agencies, including the IOM of the NAS (IOM, 2008), International Agency for Research on Cancer
27   (IARC, 2006), *EPA Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), Centers for Disease
28   Control and Prevention (CDC, 2004), and National Acid Precipitation Assessment Program (NAPAP,
29   1991). These formalized approaches offer guidance for assessing causality. The frameworks are similar in

1   nature, although adapted to different purposes, and have proven effective in providing a uniform structure

2   and language for causal determinations. Moreover, these frameworks have supported decision-making

3   under conditions of uncertainty.

1.6.1. Scientific Evidence Used in Establishing Causality

4   Causality determinations are based on the evaluation and synthesis of evidence from across

5   scientific disciplines; the type of evidence that is most important for such determinations will vary by

6   pollutant or assessment. The most compelling evidence of a causal relationship between pollutant

7   exposures and human health effects comes from human clinical studies. This type of study experimentally

8   evaluates the health effects of administered exposures in human volunteers under highly-controlled

9   laboratory conditions.

10   In epidemiologic or observational studies of humans, the investigator does not control exposures or

11   intervene with the study population. Broadly, observational studies can describe associations between

12   exposures and effects. These studies fall into several categories: cross-sectional, prospective cohort, and

13   time-series studies. "Natural experiments" offer the opportunity to investigate changes in health with a

14   change in exposure; these include comparisons of health effects before and after a change in population

15   exposures, such as closure of a pollution source.

16   Experimental animal data complement the clinical and observational data; these studies can help

17   characterize effects of concern, exposure-response relationships, susceptible subpopulations and MOAs.

18   In the absence of clinical or epidemiologic data, animal data alone may be sufficient to support a likely

19   causal determination, assuming that humans respond similarly to the experimental species.

1.6.2. Association and Causation

20   "Cause" is a significant, effectual relationship between an agent and an effect on health or public

21   welfare. "Association" is the statistical dependence among events, characteristics, or other variables. An

22   association is prima facie evidence for causation; alone, however, it is insufficient proof of a causal

23   relationship between exposure and disease. Unlike an association, a causal claim supports the creation of

24   counterfactual claims; that is, a claim about what the world would have been like under different or

25   changed circumstances (IOM, 2008). Much of the newly available health information evaluated in this

26   ISA comes from epidemiologic studies that report a statistical association between ambient exposure and

27   health outcome.

28   Many of the health and environmental outcomes reported in these studies have complex etiologies.

29   Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated by multiple

1 agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status,
2 immune competence, and social factors (Gee and Payne-Sturges, 2004; IOM, 2008). Effects on
3 ecosystems are often also multifactorial with a complex web of causation. Further, exposure to a
4 combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk represents
5 the net effect of many actions and counteractions.

1.6.3. Evaluating Evidence for Inferring Causation

6   Moving from association to causation involves elimination of alternative explanations for the
7 association. In estimating the causal influence of an exposure on health or environmental effects, it is
8 recognized that scientific findings incorporate uncertainty. Uncertainty can be defined as a state of having
9 limited knowledge where it is impossible to exactly describe an existing state or future outcome; e.g., the
10 lack of knowledge about the correct value for a specific measure or estimate. Uncertainty characterization
11 and uncertainty assessment are two activities that lead to different degrees of sophistication in describing
12 uncertainty. Uncertainty characterization generally involves a qualitative discussion of the thought
13 processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. The uncertainty
14 assessment is more quantitative. The process begins with simpler measures (e.g., ranges) and simpler
15 analytical techniques and progresses, to the extent needed to support the decision for which the
16 assessment is conducted, to more complex measures and techniques. Data will not be available for all
17 aspects of an assessment and those data that are available may be of questionable or unknown quality. In
18 these situations, evaluation of uncertainty can include professional judgment or inferences based on
19 analogy with similar situations. The net result is that the assessments will be based on a number of
20 assumptions with varying degrees of uncertainty.
21   Uncertainties commonly encountered in evaluating health evidence for the criteria air pollutants are
22 outlined below for epidemiologic and experimental studies. Various approaches to characterizing
23 uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis,
24 in order of increasing complexity and data requirements. The ISA generally evaluates uncertainties
25 qualitatively in assessing the evidence from across studies; in some situations quantitative analysis
26 approaches, such as meta-regression may be used.
27   Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants in a
28 highly controlled laboratory setting. Also referred to as human clinical studies, these experiments allow
29 investigators to expose subjects to known concentrations of air pollutants under carefully regulated
30 environmental conditions and activity levels. In some instances, controlled human exposure studies can
31 also be used to characterize concentration-response relationships at pollutant concentrations relevant to
32 ambient conditions. Controlled human exposures are typically conducted using a randomized crossover

1   design with subjects exposed both to CO and a clean air control. In this way, subjects serve as their own

2   controls, effectively controlling for many potential confounders. However, human clinical studies are

3   limited by a number of factors including a small sample size and short exposure time. The repetitive

4   nature of ambient CO exposures at levels that can vary widely may lead to cumulative health effects, but

5   this type of exposure is not practical to replicate in a laboratory setting. In addition, although subjects do

6   serve as their own controls, personal exposure to pollutants in the hours and days preceding the controlled

7   exposures may vary significantly between and within individuals. Finally, human clinical studies require

8   investigators to adhere to stringent health criteria for a subject to be included in the study, and therefore

9   the results cannot necessarily be generalized to an entire population. Although some human clinical

10   studies have included health-compromised individuals such as asthmatics or individuals with chronic

11   obstructive pulmonary disease (COPD) or coronary artery disease (CAD), these individuals must also be

12   relatively healthy and do not represent the most sensitive individuals in the population. Thus, a lack of

13   observation of effects from human clinical studies does not necessarily mean that a causal relationship

14   does not exist. While human clinical studies provide important information on the biological plausibility

15   of associations observed between air pollutant exposure and health outcomes in epidemiologic studies,

16   observed effects in these studies may underestimate the response in certain subpopulations.

17   Epidemiologic studies provide important information on the associations between health effects

18   and exposure of human populations to ambient air pollution. These studies also help to identify

19   susceptible or vulnerable subgroups and associated risk factors. There are important methodological

20   issues to be considered in evaluating results from air pollution epidemiologic studies, especially the

21   potential for confounding and/or effect modification; and exposure measurement error.

22   Scientific judgment is needed regarding sources and magnitude of potential confounding by

23   covariates, together with judgment about how well the existing constellation of study designs, results, and

24   analyses address this potential threat to inferential validity. One key consideration is evaluation of the

25   potential contribution of CO to health effects when it is a component of a complex air pollutant mixture.

26   There are multiple ways by which CO might cause or be associated with adverse health effects. First, the

27   reported CO effect estimates in epidemiologic studies may reflect independent CO effects on health.

28   Second, ambient CO may be serving as an indicator of complex ambient air pollution mixtures that share

29   the same source as CO (e.g., motor vehicle emissions). Finally, copollutants may mediate the effects of

30   CO, or CO may influence the toxicity of copollutants.

31   Epidemiologists use the term "interaction" or "effect modification" to denote the departure from

32   the observed joint risk from what might be expected based on the separate effects of the factors. In

33   addition, confounding can result in the production of an association between adverse health effects and

34   CO that is actually attributable to another factor that is associated with CO in a particular study.

35   Multivariate models are the most widely used strategy to address confounding in epidemiologic studies,

1 but such models are not always easily interpreted when assessing effects of covarying pollutants such as

2 fine particulate matter ($PM_{2.5}$) and NO_2.

3   Inferring causation requires consideration of potential confounders. In confounding, the apparent

4 effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or

5 mixed with the actual exposure effect, which may be null. When associations are found in epidemiologic

6 studies, one approach to remove spurious associations from possible confounders is to control for

7 characteristics that may differ between exposed and unexposed persons; this is frequently termed

8 "adjustment." Multivariable regression models constitute one tool for estimating the association between

9 exposure and outcome after adjusting for characteristics of participants that might confound the results.

10 The use of multipollutant regression models has been the prevailing approach for controlling potential

11 confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant

12 from multipollutant regression models is made difficult by the possibility that one or more air pollutants

13 may be acting as a surrogate for an unmeasured or poorly-measured pollutant or for a particular mixture

14 of pollutants. Further, the correlation between the air pollutant of interest and various copollutants may

15 show temporal and spatial discongruities that can influence exposures and health effects. Thus, results of

16 models that attempt to distinguish gaseous and particle effects must be interpreted with caution. Despite

17 these limitations, the use of multipollutant models is still the prevailing approach employed in most air

18 pollution epidemiologic studies and may provide some insight into the potential for confounding or

19 interaction among pollutants.

20   Another way to adjust for potential confounding is through stratified analysis, i.e., examining the

21 association within homogeneous groups with respect to the confounding variable. Stratified analysis can

22 also be used to examine potential effect modification. The use of stratified analyses has an additional

23 benefit: it allows examination of effect modification through comparison of the effect estimates across

24 different groups. If investigators successfully measured characteristics that distort the results, adjustment

25 of these factors help separate a spurious from a true causal association. Appropriate statistical adjustment

26 for confounders requires identifying and measuring all reasonably expected confounders. Deciding which

27 variables to control for in a statistical analysis of the association between exposure and disease depends

28 on knowledge about possible mechanisms and the distributions of these factors in the population under

29 study. Identifying these mechanisms makes it possible to control for potential sources that may result in a

30 spurious association.

31   Measurement error is another problem encountered when adjusting for spurious associations.

32 Controlling for confounders, whether by adjustment or stratification, is only successful when the

33 confounder is well-measured. Considered together, the effects of a well-measured covariate may be

34 overestimated in contrast to a covariate measured with greater error. There are several components that

35 contribute to exposure measurement error in these studies, including the difference between true and

36 measured ambient concentrations, the difference between average personal exposure to ambient pollutants

1   and ambient concentrations at central monitoring sites, and the use of average population exposure rather
2   than individual exposure estimates. Previous assessments have examined the role of measurement error in
3   time-series epidemiologic studies using simulated data and mathematical analyses and suggested that
4   "transfer of effects" would only occur under unusual circumstances (e.g., "true" predictors having high
5   positive or negative correlation; substantial measurement error; or extremely negatively correlated
6   measurement errors) (U.S. EPA, 2004).

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

14   In addition to clinical and epidemiologic studies, the tools of experimental biology have been
15   valuable for developing insights into human physiology and pathology. Laboratory tools have been
16   extended to explore the effects of putative toxicants on human health, especially through the study of
17   model systems in other species. Background knowledge of the biological mechanisms by which an
18   exposure might or might not cause disease can prove crucial in establishing, or negating, a causal claim.
19   Testable hypotheses about the causal nature of proposed mechanisms or modes of action are central to
20   utilizing experimental data in causal determinations.

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

1.6.4. Application of Framework for Causal Determination

1   EPA uses a two-step approach to evaluate the scientific evidence on health or environmental effects

2   of criteria pollutants. The first step determines the weight of evidence in support of causation and

3   characterizes the strength of any resulting causal classification. The second step includes further

4   evaluation of the quantitative evidence regarding the concentration-response relationships and the loads or

5   levels, duration and pattern of exposures at which effects are observed.

6   To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and

7   scientists. The most widely cited aspects of causality in epidemiology, and public health, in general, were

8   articulated by Sir Austin Bradford Hill in 1965 and have been widely used (CDC, 2004; IARC, 2006;

9   IOM, 2008; U.S. EPA, 2005, 2008d). Several adaptations of the Hill aspects have been used in aiding

10   causality judgments in the ecological sciences (Adams, 2003; Buck et al., 2000; Collier, 2003; Fox, 1991;

11   Gerritsen et al., 1998). These aspects (Hill, 1965) have been modified (Table 1-1) for use in causal

12   determinations specific to health and welfare effects or pollutant exposures (U.S. EPA, 2008f).[2] Some

13   aspects are more likely than others to be relevant for evaluating evidence on the health or environmental

14   effects of criteria air pollutants. For example, the analogy aspect does not always apply, especially for the

15   gaseous criteria pollutants, and specificity would not be expected for multi-etiologic health outcomes,

16   such as asthma or cardiovascular disease, or ecological effects related to acidification. Aspects that

17   usually play a larger role in determination of causality are consistency of results across studies, coherence

18   of effects observed in different study types or disciplines, biological plausibility, exposure-response

19   relationship, and evidence from "natural" experiments.

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.

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

[2] The Hill 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.

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

1   While these aspects provide a framework for assessing the evidence, they do not lend themselves to

2   being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about

3   causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically

4   significant results or statistically nonsignificant results and reach credible conclusions about the relative

5   weight of the evidence and the likelihood of causality. Rather, these important considerations are taken

6   into account with the goal of producing an objective appraisal of the evidence, informed by peer and

7   public comment and advice, which includes weighing alternative views on controversial issues.

8   Additionally, it is important to note that the aspects in Table 1-1 cannot be used as a strict checklist, but

9   rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or

10   more of the principles does not automatically preclude a determination of causality (e.g., see discussion in

11   (CDC, 2004).

1.6.5. Determination of Causality

12   In the ISA, EPA assesses the results of recent relevant publications, building upon evidence

13   available during the previous NAAQS review, to draw conclusions on the causal relationships between

14   relevant pollutant exposures and health or environmental effects. This ISA uses a five-level hierarchy that

15   classifies the weight of evidence for causation, not just association[1]; that is, whether the weight of

16   scientific evidence makes causation at least as likely as not, in the judgment of the reviewing group. In

17   developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the

18   IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2008), EPA's

19   Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), and the U.S. Surgeon General's smoking

20   reports (CDC, 2004). In the ISA, EPA uses a series of five descriptors to characterize the weight of

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

1   evidence for causality (U.S. EPA, 2008d, f). This weight of evidence evaluation is based on various lines

2   of evidence from across the health and environmental effects disciplines. These separate judgments are

3   integrated into a qualitative statement about the overall weight of the evidence and causality. The five

4   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 between relevant pollutant exposures and the health outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Evidence includes, for example, controlled human exposure studies; or observational studies that cannot be 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 between relevant pollutant exposure and the outcome. Causality is supported when an association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure (laboratory or small- to medium-scale field studies) provides 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 between relevant pollutant exposures and health outcome but important uncertainties remain. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a likely causal association between relevant pollutant exposures and the outcome. 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 between relevant pollutant exposures and the health outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent.	Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an association, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists between relevant pollutant exposures and health outcome. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome.	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome.
Suggestive of no causal relationship	Evidence is suggestive of no causal relationship between relevant pollutant exposures and health outcome. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible or vulnerable subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposure.	Several adequate studies, examining relationships between relevant exposures and outcomes, are consistent in failing to show an association between exposure and the outcome at any level of exposure.

Source: U.S. EPA (2008f)

5   For the CO ISA, determination of causality involved the evaluation of evidence for different types

6   of health effects associated with short- and long-term exposure periods. In making determinations of

7   causality for CO, evidence was evaluated for health outcome categories, such as cardiovascular effects,

8   and then conclusions were drawn based upon the integration of evidence from across disciplines

9   (e.g., epidemiology, clinical studies and toxicology) and also across the suite of related individual health

10   outcomes. To accomplish this integration, evidence from multiple and various types of studies was

1   considered. Response was evaluated over a range of observations which was determined by the type of
2   study and methods of exposure or dose and response measurements. Results from different protocols were
3   compared and contrasted.

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

Effects on Human Populations

15   Important questions regarding quantitative relationships include:

16   ▪ What is the concentration-response or dose-response relationship in the human population?

17   ▪ What is the interrelationship between incidence and severity of effect?

18   ▪ What exposure conditions (dose or exposure, duration and pattern) are important?

19   ▪ What subpopulations appear to be differentially affected i.e., more susceptible or vulnerable
20   to effects?

21   Addressing these questions requires evaluating the entirety of policy-relevant quantitative evidence
22   regarding the concentration-response relationships including levels of pollutant and exposure durations at
23   which effects were observed, and subpopulations that differ in susceptibility or vulnerability from the
24   general population. This integration of evidence resulted in identification of a study or set of studies that
25   best approximated the concentration response relationship for the U.S. population, given the current state
26   of knowledge and the uncertainties that surrounded these estimates.
27   An important consideration in characterizing the public health impacts associated with exposure to
28   a pollutant is whether the concentration-response relationship is linear across the full concentration range
29   encountered, or if nonlinear relationships exist along any part of this range. Of particular interest is the
30   shape of the concentration-response curve at and below the level of the current standards. The shape of
31   the concentration-response curve varies, depending on the type of health outcome, underlying biological
32   mechanisms and dose. At the human population level, however, various sources of variability and

1 uncertainty (such as the low data density in the lower concentration range, possible influence of

2 measurement error, and individual differences in susceptibility to air pollution health effects) tend to

3 smooth and "linearize" the concentration-response function. Additionally, many chemicals and agents

4 may act by perturbing naturally occurring background processes that lead to disease, which also linearizes

5 population concentration-response relationships (Clewell and Crump, 2005; Crump et al., 1976; Hoel,

6 1980). These attributes of population dose-response may explain why the available human data at ambient

7 concentrations for some environmental pollutants (e.g., PM, O_3, lead [Pb], environmental tobacco smoke

8 [ETS], radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though

9 likely mechanisms include nonlinear processes for some key events. These attributes of human population

10 dose-response relationships have been extensively discussed in the broader epidemiologic literature

11 (Rothman and Greenland, 1998).

Effects on Ecosystems or Public Welfare

12 Key questions for understanding the quantitative relationships between exposure (or concentration

13 or deposition) to a pollutant and risk to ecosystems or the public welfare include:

14 ▪ What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations,

15 functions, etc.) appear to be affected, or are more sensitive to effects?

16 ▪ Under what exposure conditions (amount deposited or concentration, duration and pattern)

17 are effects seen?

18 ▪ What is the shape of the concentration-response or exposure-response relationship?

19 Evaluations of causality typically characterize how the probability of ecological and welfare effects

20 change in response to exposure. A challenge to the quantification of exposure-response relationships for

21 ecological effects is the variability across ecosystems. Ecological responses are evaluated within the range

22 of observations, so a quantitative relationship may be determined for a given ecological system and scale.

23 There is great regional and local variability in ecosystems, thus an exposure-response relationship

24 generally cannot be determined at the larger national or even regional scale. Quantitative relationships

25 therefore are available site by site. For example, an ecological response to deposition of a given pollutant

26 can differ greatly between ecosystems. Where results from greenhouse or animal ecotoxicological studies

27 are available, they may be used to aid in characterizing exposure-response relations, particularly relative

28 to mechanisms of action, and characteristics of sensitive biota.

1.6.6. Concepts in Evaluating Adversity of Health Effects

1   In evaluating the health evidence, a number of factors can be considered in determining the extent
2   to which health effects are "adverse" for health outcomes such as changes in lung function or in
3   cardiovascular health measures. Some health outcome events, such as hospitalization for respiratory or
4   cardiovascular diseases, are clearly considered adverse; what is more difficult is determining the extent of
5   change in the more subtle health measures that is adverse. What constitutes an adverse health effect may
6   vary between populations. Some changes in healthy individuals may not be considered adverse while
7   those of a similar type and magnitude are potentially adverse in more susceptible individuals.

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

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

1.7. Summary

28   This first external review draft ISA is a concise evaluation and synthesis of the most
29   policy-relevant science for reviewing the NAAQS, and it communicates critical science judgments
30   relevant to the NAAQS review. It reviews the most policy-relevant evidence from health and

1   environmental effects studies, including mechanistic evidence from basic biological science. Annexes to
2   the ISA provide additional details of the literature published since the last review. A framework for
3   making critical judgments concerning causality was presented in this chapter. It relies on a widely
4   accepted set of principles and standardized language to express evaluation of the evidence. This approach
5   can bring rigor and clarity to the current and future assessments. This ISA should assist EPA and others,
6   now and in the future, to accurately represent what is presently known—and what remains unknown—
7   concerning the effects of CO on human health and public welfare.

Chapter 2. Integrative Health Effects Overview

1   The subsequent chapters of this ISA present the most policy-relevant information related to the
2   review of the NAAQS for CO, including a synthesis of the evidence presented in the 2000 CO AQCD
3   with the results of more recent studies. This chapter integrates important findings from the disciplines
4   evaluated in the assessment of the CO scientific literature, which include atmospheric sciences, ambient
5   air data analyses, exposure assessment, dosimetry, and health effects research (animal toxicology,
6   controlled human exposure, and epidemiologic studies). The EPA framework for causal determinations
7   described in Chapter 1 has been applied to the body of evidence evaluated in this assessment in order to
8   characterize the relationship between exposure to CO at relevant pollutant exposures and health effects.
9   The EPA framework applied here employs a five-level hierarchy for causal determination:

10   ▪   Causal relationship

11   ▪   Likely to be a causal relationship

12   ▪   Suggestive of a causal relationship

13   ▪   Inadequate to infer a causal relationship

14   ▪   Suggestive of no causal relationship

15   This evaluation led to causal determinations for a range of health outcomes, and characterization of
16   the magnitude of these responses, including responses in susceptible or vulnerable subpopulations, over a
17   range of relevant concentrations. This integration of evidence also provides a basis for characterizing the
18   concentration-response relationships of CO and adverse health outcomes for the U.S. population, given
19   the current state of knowledge.
20   This chapter summarizes and integrates the recently available scientific evidence along with key
21   findings and conclusions from the 2000 CO AQCD that best informs consideration of the policy-relevant
22   questions that frame this assessment as presented in Chapter 1. Section 2.1 discusses the trends in ambient
23   concentrations and sources of CO and provides a brief summary of factors influencing personal exposure
24   to ambient CO. Section 2.2 summarizes CO dosimetry and pharmacokinetics and describes what is
25   known regarding the hypoxic and non-hypoxic modes of action of CO. Section 2.3 integrates the evidence
26   for studies that examined health effects related to short- and long-term exposure to CO and discusses
27   important uncertainties identified in the interpretation of the scientific evidence. Finally, Section 2.4

1   presents the public health impacts associated with exposure to CO, and includes evidence of effects in
2   potentially susceptible and vulnerable populations from CO exposure.

2.1. Ambient Concentrations, Sources, and Exposure

3   CO is formed by incomplete combustion of carbon-containing fuels and by photochemical
4   reactions in the atmosphere. Nationally, on-road mobile sources constituted more than half of total CO
5   emissions in 2002, or ~63 of ~109 million tons (MT) of total CO emissions, based on the most recent
6   publicly available data from EPA's National Emissions Inventory (NEI). On-road mobile source emissions
7   decreased by 16% since 1997, which is the most recent year covered in the 2000 CO AQCD. In
8   metropolitan areas in the U.S., as much as 70-75% of all CO emissions result from on-road vehicle
9   exhaust. The majority of these on-road CO emissions are derived from gasoline-powered vehicles since
10   diesel vehicles emit relatively little CO. When emissions from incomplete combustion of fuels powering
11   non-road mobile sources, such as farm and construction equipment, lawnmowers, boats, ships,
12   snowmobiles, and aircraft are included, all mobile sources accounted for ~80% of total CO emissions in
13   the U.S. in 2002. Other sources of CO include wildfires, controlled vegetation burning, residential
14   biomass combustion, and industrial processes. While CO emissions from non-road mobile sources, fire,
15   and industry have remained fairly constant, on-road mobile source CO emissions have decreased by
16   roughly 5% per year since the early 1990s.
17   Significant reductions in ambient CO concentrations and in the number of NAAQS exceedances
18   have been observed over the past 25 years, a continuation of trends documented in the 2000 CO AQCD.
19   Nationwide ambient CO data from the EPA Air Quality System (AQS), for the years 2005-2007, show
20   that the median 1-h daily maximum (max) concentration across the U.S. was 0.7 ppm; the mean was
21   0.9 ppm; the 95th percentile was 2.4 ppm; and the 99th percentile was 3.8 ppm. The median 8-h daily
22   max ambient CO concentration for the years 2005-2007 was 0.5 ppm; the mean was 0.7 ppm; the 95th
23   percentile was 1.7 ppm; and the 99th percentile was 2.6 ppm. The current CO NAAQS are 35 ppm (1-h
24   avg) and 9 ppm (8-h avg), not to be exceeded more than once per year (yr). During the years 2005-2007,
25   1-h and 8-h CO concentrations did not exceed the NAAQS level more than once per year at any
26   monitoring site. Moreover, in these 3 years, a 1-h avg concentration in excess of 35 ppm was reported
27   only once, in 2007, in Ogden, UT (39 ppm), and there were only 7 reported 8-h avg values nationwide in
28   excess of 9 ppm in all 3 years. Seasonally divided box plots of data from 2005-2007 compiled for
29   spatially diverse urban metropolitan areas illustrate the tendency for higher median CO concentrations
30   and wider variations in concentrations in the winter and fall compared with the spring and summer.
31   Policy-relevant background (PRB) concentrations of CO were computed for this assessment using
32   data for the years 2005-2007 collected at 12 remote sites in the U.S. which are part of the National

1   Oceanic and Atmospheric Administration's (NOAA) Global Monitoring Division (GMD) and are not part

2   of the EPA national regulatory network. The 3-year avg CO PRB averaged ~0.13 ppm in Alaska,

3   ~0.10 ppm in Hawaii, and ~0.13 ppm over the contiguous U.S. (CONUS). (Note that the analysis for

4   North American PRB in this assessment was made by segregating the three Alaska sites based on their

5   high latitude and the two Hawaii sites based on their distance from the continent and then treating the

6   remaining seven sites as representative of the CONUS PRB.)

7   A person's total personal exposure to CO is a combination of ambient and non-ambient exposures.

8   Ambient exposure can be further broken down into direct exposure while outdoors and exposure to

9   ambient CO which has infiltrated into buildings and vehicles. Several studies have shown that in the

10 absence of indoor sources such as ETS or gas stoves, CO concentrations are highest in automobiles and

11 near highly traveled roadways. Specific concentrations vary as a function of vehicle ventilation rate and

12 CO emissions source strength and are related to, for example, on-road vehicle numbers and speed. In-

13 vehicle CO concentrations are typically reported to be between 2 and 5 times higher than ambient

14 concentrations measured at the roadside, but have been reported to be as much as 25 times higher. A

15 portion of these high concentrations comes from the vehicle's own engine emissions entrained with the

16 ambient concentrations from the roadway, although the exact fraction of this self-pollution in the in-

17 vehicle total varies with body integrity of the vehicle and is not known with certainty. Concentrations of

18 CO, like those of other on-road vehicle pollutants, often display an inverse relationship with distance

19 from the roadway. For CO, this fall-off with distance can be very sharp up to ~70 meters (m), beyond

20 which the concentration increment from roadway emissions is largely indistinguishable from local

21 ambient concentrations. The siting and location instructions for federal regulatory CO monitors explicitly

22 recognize the need to measure at distances close to mobile sources with a requirement for monitored areas

23 that at least one monitor be sited to measure max concentration. This is often accomplished with a

24 monitor situated at the CFR-defined microscale of 2-10 m from the roadway; these microscale monitors

25 also have sample inlets mounted at 3 ± 0.5 m above ground level (AGL), unlike those at larger scale

26 distances whose inlet heights can vary between 2 and 15 m AGL. In 2007, there were at least 70 CO

27 monitors described as microscale reporting to AQS.

28   Although the correlations across CO monitors sited to sample at different scales can be greater than

29 0.8 in some areas, they also can vary widely from within and between cities across the U.S. as a function

30 of natural and urban topography, meteorology, and strength and proximity to sources. At the same time,

31 personal exposure monitoring captures both ambient and non-ambient CO concentrations. Because

32 non-ambient CO exposure is not expected to be correlated with ambient CO concentrations at the

33 monitor, the non-ambient contribution to total personal CO exposure complicates interpretation of health

34 effects relationships observed in epidemiologic studies. For the general U.S. population, exposure error

35 analysis for epidemiologic studies, as summarized in Chapter 3, indicates that fixed-site measured

36 ambient CO concentration is generally a good indicator of ambient exposure to CO.

2.2. Dosimetry, Pharmacokinetics, and Mode of Action

2.2.1. Dosimetry and Pharmacokinetics

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

2.2.2. Mode of Action

22   The diverse effects of CO are dependent upon dose, duration of exposure, and the cell types and
23   tissues involved. Responses to CO are not necessarily due to a single process and may instead be
24   mediated by a combination of effects including COHb-mediated hypoxic stress and mechanisms unrelated
25   to tissue hypoxia including free radical production and the initiation of cell signaling. However binding of
26   CO to reduced iron in heme proteins with subsequent alteration of heme protein function is the underlying
27   mechanism for both the hypoxic and non-hypoxic biological responses to CO.

1   As discussed in the 2000 CO AQCD, the most well-known pathophysiological effect of CO is
2   tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the
3   O_2-carrying capacity of blood, but it also impairs the release of O_2 from O_2Hb. Compensatory alterations
4   in hemodynamics, such as vasodilation and increased cardiac output, protect from tissue hypoxia. At
5   ambient CO concentrations, these compensatory changes are slight and likely tolerable in people with a
6   healthy cardiovascular system. However, people with cardiovascular detriments may be unable to endure
7   these small changes in hemodynamics which may lead to the presentation of health effects as described in
8   Sections 5.2.1 and 5.2.2. Binding of CO to Mb, as discussed in the 2000 CO AQCD and in Section
9   4.3.2.3, can also impair the delivery of O_2 to tissues. Mb has a high affinity for CO; however,
10   physiological effects are seen only after high dose exposures to CO, resulting in COMb concentrations far
11   above baseline levels.
12   Non-hypoxic mechanisms underlying the biological effects of CO have been the subject of a
13   substantial amount of recent research since the 2000 CO AQCD. Most of these mechanisms are related to
14   CO's ability to bind heme-containing proteins other than Hb and Mb. These mechanisms, which may be
15   interrelated, include alteration in nitric oxide (NO) signaling, inhibition of cytochrome *c* oxidase, heme
16   loss from proteins, disruption of iron homeostasis, and alteration in cellular redox status. CO is a
17   ubiquitous cell signaling molecule and the physiological functions of HO-derived CO are numerous. The
18   endogenous generation and release of CO from HO-1 and HO-2 is tightly controlled, as is any
19   homeostatic process. Thus, exogenously-applied CO has the capacity to disrupt myriad heme-based
20   signaling pathways due to its nonspecific nature. Only a limited amount of information is available
21   regarding the impact of exogenous CO on tissue and cellular levels of CO. However recent animal studies
22   demonstrated increased tissue CO levels and biological responses following exposure to 50 ppm CO.
23   Whether or not environmentally relevant exposures to CO can affect endogenous CO signaling pathways
24   and lead to adverse health effects is an open question for which there are no definitive answers at this
25   time.

2.3. Health Effects

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

Outcome Category	Exposure Period	Causality Determination
Cardiovascular morbidity	Short-term	Likely to be 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	Suggestive of no causal relationship

2.3.1. Cardiovascular Morbidity

1   The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb
2   levels relevant to the current NAAQS comes from a series of controlled human exposure studies among
3   individuals with CAD (see Section 5.2). These studies, described in the 1991 and 2000 CO AQCDs,
4   demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes
5   following CO exposures resulting in COHb levels of 3-6%, with one multicenter study reporting similar
6   effects at COHb levels as low as 2.4%. No human clinical studies have evaluated the effect of controlled
7   exposures to CO resulting in COHb levels lower than 2.4%. Human clinical studies published since the
8   2000 CO AQCD have reported no association between CO and ST-segment changes or arrhythmia;
9   however, none of these studies included individuals with diagnoses of heart disease.
10   While the exact physiological significance of the observed ST-segment changes among individuals
11   with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also
12   important to note that the individuals with CAD who participated in these controlled exposure studies
13   were not representative of the most sensitive individuals in the population. In fact, the most sensitive
14   individuals may respond to levels of COHb lower than 2.4%. Variability in activity patterns and severity
15   of disease among individuals with CAD is likely to influence the critical level of COHb which leads to
16   adverse cardiovascular effects.
17   The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also
18   vary between individuals. First of all, endogenous CO production varies as described in Section 4.5, but
19   generally results in less than 1% COHb. Secondly, nonambient exposures to CO, such as exposure to
20   ETS, can increase COHb above baseline levels. Ambient exposures will result in an additive increase in

1   COHb. Using mathematical modeling to predict changes in COHb in healthy inactive adults (Quantitative

2   Circulatory Physiology [QCP] model, Section 4.2.3), it can be estimated that exposure to 35 ppm CO for

3   1 h results in an increase of 0.6% COHb over baseline and exposure to 9 ppm CO for 8 h results in an

4   increase of 0.8% COHb over baseline. Furthermore, 24-h exposure to 3 ppm CO results in an increase of

5   0.4% COHb above baseline which can also be obtained following 1-h exposure to 30 ppm CO.

6   Consequently, exposure to CO at concentrations relevant to the NAAQS has the potential to increase

7   COHb to levels associated with adverse cardiovascular health effects in some individuals.

8   Findings of controlled human exposure studies are coherent with findings of recent epidemiologic

9   studies conducted since the 2000 CO AQCD, which observed associations between ambient CO

10 concentration and emergency department (ED) visits and hospital admissions for ischemic heart disease

11 (IHD), congestive heart failure (CHF) and all-cause cardiovascular disease (CVD). All but one of these

12 epidemiologic studies were conducted in locations where the entire distribution of CO concentrations

13 were at or below the level of the current NAAQS, with mean 24-h avg concentrations ranging from

14 0.5 ppm (Montreal, Canada) to 9.4 ppm (Tehran, Iran) (Table 5-7). A single study reported a negative

15 association between CO concentration and hospital admissions and ED visits for IHD among all ages; all

16 other associations were positive, with increases in hospital admissions and ED visits for IHD between

17 0.2% and 19.8% per standardized increase in CO concentration (Figure 5-1). These recent studies build

18 upon the conclusions of the 2000 CO AQCD that short-term variations in ambient CO concentrations are

19 associated with daily hospital admissions for heart disease.

20   These health outcomes are consistent with a role for CO in limiting O_2 availability (i.e., hypoxic

21 mechanisms) in individuals with CAD. However, recent toxicological studies suggested that CO may also

22 act through non-hypoxic mechanisms by disrupting cellular signaling. Studies in healthy animals

23 demonstrated oxidative injury and inflammation in response to 50-100 ppm CO while studies in disease

24 models demonstrate effects on heart rhythm and exacerbation of cardiomyopathy and vascular remodeling

25 in response to 35-50 ppm CO. Furthermore, in utero exposure to 150 ppm CO alters postnatal

26 elecrophysiological maturation in rat cardiomyocytes. Further investigations will be useful in determining

27 the importance of non-hypoxic mechanisms following environmentally-relevant CO exposures. Taken

28 together, the evidence from epidemiologic, human clinical, and toxicological studies is **sufficient to**

29 **conclude that a causal relationship is likely to exist between relevant short-term CO exposures and**

30 **cardiovascular morbidity.**

2.3.2. Central Nervous System Effects

31   Exposure to high levels of CO has long been known to adversely affect CNS function, with

32 symptoms following acute CO poisoning including headache, dizziness, cognitive difficulties,

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

10   Toxicological studies that were not discussed in the 2000 CO AQCD employed rodent models to
11   show that low level CO exposure during the in utero period can adversely affect adult outcomes including
12   behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system (discussed in
13   Section 5.3). In utero CO exposure, including both intermittent and continuous exposure, has been shown
14   to impair multiple behavioral outcomes in offspring including active avoidance behavior (150 ppm CO),
15   non-spatial memory (75 and 150 ppm CO), spatial learning (endogenous CO inhibition), homing behavior
16   (150 ppm CO), locomotor movement (150 ppm CO), and negative geotaxis (125 and 150 ppm). In two
17   separate studies, in utero CO exposure (75 and 150 ppm) was associated with significant myelination
18   decrements without associated changes in motor activity in adult animals. Multiple studies demonstrated
19   that in utero CO exposure affected glutamatergic, cholinergic, catecholaminergic, and dopaminergic
20   neurotransmitter levels or transmission in exposed male rodents. Possible or demonstrated adverse
21   outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include respiratory
22   dysfunction (200 ppm CO), impaired sexual behavior (150 ppm CO), and an adverse response to
23   hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal CO exposure has been
24   shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood.
25   This is manifested with atrophy of cochlear cells innervating the inner hair cells (25 ppm CO), decreased
26   immunostaining associated with impaired neuronal activation (12.5 ppm CO), impaired myelination of
27   auditory associated nerves (25 ppm CO), decreased energy production in the sensory cell organ of the
28   inner ear or the organ of corti (25 ppm CO), some of which is mechanistically proposed to be mediated by
29   reactive oxygen species (ROS) (25 ppm CO). Functional tests of the auditory system of neonatally, low
30   level CO-exposed rodents, using otoacoustic emissions (OAE) testing (50 ppm CO) and amplitude
31   measurements of the 8th cranial nerve action potential (12, 25, 50, 100 ppm CO), revealed decrements in
32   auditory function at PND22 and permanent changes into adulthood using AP testing (50 ppm CO).
33   Together, these animal studies demonstrate that in utero exposure to CO can adversely affect adult
34   behavior, neuronal myelination, neurotransmission, and the auditory system in adult male rodents.
35   Considering the combined evidence from controlled human exposure and toxicological studies, the

1   evidence is **suggestive of a causal relationship between relevant short- and long-term CO exposures**
2   **and central nervous system effects.**

2.3.3. Birth Outcomes and Developmental Effects

3   The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for
4   preterm birth (PTB) and cardiac birth defects. These outcomes were not addressed in the 2000 CO
5   AQCD, which included only two studies that examined the effect of ambient CO on low birth weight
6   (LBW). Since then, a number of studies have been conducted looking at varied outcomes, including PTB,
7   birth defects, fetal growth (including LBW), and infant mortality.
8   There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first
9   trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB
10   outcome were conducted in California, and these reported consistent results whereby all studies reported a
11   significant association with CO exposure during early pregnancy, and exposures were assigned from
12   monitors within close proximity of the mother's residential address. Additional studies conducted outside
13   of the U.S. provide supportive, though less consistent, evidence of an association between CO
14   concentration and PTB.
15   Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these
16   studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects.
17   This insult to the heart is coherent with results of human clinical studies demonstrating the heart as a
18   target for CO effects (Section 5.2). Animal toxicological studies provide additional evidence for such an
19   insult to the heart, and reported transient cardiomegaly at birth after continuous in utero CO exposure (60,
20   125, 250 and 500 ppm CO), delayed myocardial electrophysiolgical maturation (150 ppm CO), or
21   systemic splenic immunocompromise (75 or 150 ppm CO). Toxicological studies have also shown that
22   exogenous continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a
23   dose-dependent manner that was further exacerbated by dietary protein restriction (65 ppm CO) or zinc
24   depletion (500 ppm CO). Toxicological studies of exogenous CO exposure over the duration of gestation
25   have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in
26   prenatally exposed offspring.
27   There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal
28   growth in epidemiologic studies. In general, the reviewed studies, summarized in Figures 5-7 through 5-9,
29   reported small reductions in birth weight (ranging ~5-20 g). Several studies examined various
30   combinations of birth weight, LBW, and small for gestational age (SGA)/intrauterine growth restriction
31   (IUGR) and inconsistent results are reported across these metrics. It should be noted that having a
32   measurable, even if small, change in a population is different than having an effect on a subset of

1 susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related

2 to a small change in birth weight in all births across the population, or a marked effect in some subset of

3 births.

4 In general, there is limited epidemiologic evidence that CO is associated with an increased risk of

5 infant mortality during the neonatal or post-neonatal periods. In support of this limited evidence, animal

6 toxicological studies do provide some evidence that exogenous CO exposure to pups in utero significantly

7 increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and

8 prenatal mortality (7 h/day, 250 ppm CO).

9 Evidence exists for additional developmental outcomes which have been examined in toxicological

10 studies, but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and

11 memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system.

12 Structural aberrations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and

13 auditory related nerves (25 ppm CO) were seen in pups after in neonatal CO exposure. Auditory

14 functional testing using OAE (50 ppm CO) and ABR (12, 25, 50, 100 ppm CO) on rodents exposed

15 perinataly to CO showed that CO-exposed neonates had auditory decrements at PND22 (OAE and ABR)

16 and permanent changes into adulthood with ABR (50 ppm CO).

17 Overall, there is limited, though positive, epidemiologic evidence for a CO-induced effect on PTB

18 and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and

19 infant mortality. Animal toxicological studies provide support and coherence for these effects. Both

20 hypoxic and non-hypoxic mechanisms that could lead to such effects have been proposed in the

21 toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying

22 reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for

23 some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these

24 associations in animal toxicological studies, the evidence is **suggestive of a causal relationship**

25 **between long-term exposures to relevant CO concentrations and developmental effects and birth**

26 **outcomes.**

2.3.4. Respiratory Morbidity

27 New epidemiologic studies, supported by the body of literature summarized in the 2000 CO

28 AQCD, provide evidence of positive associations between short-term exposure to CO and respiratory-

29 related outcomes including pulmonary function, respiratory symptoms, medication use, hospital

30 admissions, and ED visits (discussed in Section 5.5). However, the interpretation of the results from

31 epidemiologic studies is difficult due to the lack of extensive copollutant analyses along with the

32 moderate to high correlation between CO and other combustion/traffic generated pollutants. To date the

1   majority of the literature has not extensively examined the association between CO and respiratory
2   morbidity due to studies focusing primarily on effects associated with exposure to other criteria
3   pollutants, namely PM and O_3. This has contributed to the inability to disentangle the effects attributed to
4   CO from the larger complex air pollution mix. In addition, uncertainty as to a biological mechanism to
5   explain the respiratory-related effects observed in the epidemiologic literature further complicates the
6   interpretation of these results, especially considering the low ambient CO concentrations reported (24-h
7   avg: 0.35–2.1 ppm). However, animal toxicological studies do provide some evidence that short-term
8   exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular
9   remodeling. Human clinical studies have not extensively examined the effect of short-term exposure to
10   CO on respiratory morbidity, specifically pulmonary function. The limited number of clinical studies that
11   have been conducted prior to and since the 2000 CO AQCD provide very little evidence of any adverse
12   effect of CO on the respiratory system at COHb levels <10%. Although human clinical studies have not
13   provided evidence to support CO-related respiratory health effects, the epidemiologic studies that
14   examined the effects of short-term exposure to CO and lung-related outcomes show positive associations
15   and animal toxicological studies demonstrate the potential for an underlying biological mechanism, which
16   together provide evidence that is **suggestive of a causal relationship between short-term exposure to**
17   **relevant CO concentrations and respiratory morbidity.**
18   Currently, only a few studies have been conducted that examine the association between long-term
19   exposure to CO and respiratory morbidity. Although some studies did observe associations between long-
20   term exposure to CO and respiratory health outcomes key uncertainties still exist. These uncertainties
21   include: the lack of replication and validation studies to evaluate new methodologies (i.e.,
22   Deletion/Substitution/Addition (DSA) algorithm) that have been used to examine the association between
23   long-term exposure to CO and respiratory health effects; whether the respiratory health effects observed
24   in response to long-term exposure to CO can be explained by the proposed biological mechanisms; and
25   the lack of co-pollutant analyses to disentangle the respiratory effects associated with CO due to its high
26   correlation with NO_2 and other combustion-related pollutants. Overall, the evidence available is
27   **inadequate to conclude that a causal relationship exists between long-term exposure to relevant**
28   **CO concentrations and respiratory morbidity.**

2.3.5. Mortality

29   Among the gaseous pollutants examined in time-series mortality studies, CO is the least frequently
30   studied criteria air pollutant. Because CO was mostly treated as a potential confounder in these studies,
31   the information available regarding the nature of the association between short-term exposure to CO and
32   mortality is limited compared to the other pollutants. However, the recently available multi-city studies,

1 which consist of larger sample sizes, and single-city studies generally confirmed the findings reported in

2 the 2000 CO AQCD (see Section 5.6).

3   The multi-city studies report comparable CO mortality risk estimates for total (non-accidental)

4 mortality with the APHEA2 European multi-city study showing slightly higher estimates for

5 cardiovascular mortality in single-pollutant models. However, when examining potential confounding by

6 copollutants these studies consistently showed that CO mortality risk estimates were reduced when NO_2

7 was included in the model, but this observation may not be "confounding" in the usual sense in that NO_2

8 may also be a surrogate marker of other pollutants or pollution sources (i.e., traffic).

9   Only one of the multi-city studies focused specifically on the CO-mortality association (the

10 APHEA study), examining: (1) model sensitivity; (2) the CO-mortality concentration-response (C-R)

11 relationship; and (3) potential effect modifiers of CO mortality risk estimates. The APHEA2 study

12 performed a sensitivity analysis, which indicated an approximate 50 - 80% difference in CO risk

13 estimates from a reasonable range of alternative models. In addition, the study examined the CO-mortality

14 C-R relationship through a grid search of varying threshold points, and found only weak evidence of a CO

15 threshold at 0.5 mg/m^3 (0.43 ppm), but this result is complicated by the lowest 10% of the CO distribution

16 for seven of the 19 cities examined being at or above 2 mg/m^3 (1.74 ppm). The examination of a variety

17 of city-specific variables to identify potential effect modifiers of the CO-mortality relationship found that

18 geographic region explained most of the heterogeneity in CO mortality risk estimates with the

19 CO-mortality associations being stronger in western and southern European cities than eastern cities. A

20 similar pattern has been reported for black smoke (BS) and SO_2 in previous APHEA studies, but the

21 geographic variability observed does not provide specific information which could be used to evaluate the

22 CO-mortality association.

23   The results from the single-city studies evaluated are generally consistent with the multi-city

24 studies in that some evidence of a positive association was found for mortality upon short-term exposure

25 to CO. However, the CO-mortality associations were often, but not always, attenuated when other

26 copollutants were included in the regression models. In addition, limited evidence was available to

27 identify cause-specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-

28 term exposure to CO.

29   The new multi- and single-city studies evaluated provide evidence that an association between

30 short-term exposure to CO and mortality exists, but limited evidence is available to evaluate cause-

31 specific mortality outcomes associated with CO exposure and it is unclear if CO is acting alone or as a

32 surrogate for other combustion-related pollutants. In addition, the results also underscore the limitation of

33 current analytical methods to disentangle the health effects associated with one pollutant in the complex

34 air pollution mixture. Overall, the epidemiologic evidence is **suggestive of a causal relationship**

35 **between short-term exposure to relevant CO concentrations and mortality.**

1   The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD that investigated
2   the association between long-term exposure to CO and mortality consistently found null or negative
3   mortality risk estimates. No such studies were discussed in the 2000 CO AQCD. The re-analysis of the
4   American Cancer Society (ACS) data by Jerrett et al. (2003) found no association between long-term
5   exposure to CO and mortality. Similar results were obtained in an updated analysis conducted by the
6   original ACS investigators when using earlier (1980) CO data, but negative associations were found when
7   using more recent (1982-1998) data. The Women's Health Initiative (WHI) Study also found no
8   association between CO and CVD events (including mortality) using the data from recent years
9   (1994-1998), while the series of Veterans Cohort studies found no association or a negative association
10   between mean annual 95th percentile of hourly CO values and mortality. In addition, a cross-sectional
11   study of U.S. counties reported results that are generally consistent with the cohort studies: positive
12   associations between long-term exposure to $PM_{2.5}$ and sulfate (SO_4^{2-}) and mortality, and generally
13   negative associations with CO. Overall, the consistent null and negative associations observed across
14   epidemiologic studies which included cohort populations encompassing potentially susceptible
15   subpopulations (i.e., post-menopausal women and hypertensive men) combined with (1) the lack of
16   evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and
17   (2) the absence of a proposed mechanism to explain the progression to mortality following long-term
18   exposure to CO provide supportive evidence that is **suggestive of no causal relationship between long-**
19   **term exposure to relevant CO concentrations and mortality**.

2.4. Public Health Impacts

2.4.1. Concentration-Response Relationship

20   Currently, very limited information is available in the human clinical and epidemiologic literature
21   regarding the CO C-R relationship and the potential presence of a CO threshold. Two human clinical
22   studies described in the 2000 CO AQCD have evaluated the C-R relationship between CO and onset of
23   exercise-induced angina among individuals with CAD, but at the high end of CO concentrations (i.e., CO
24   levels above the current NAAQS). Anderson et al. (1973) exposed 10 adult men with stable angina for 4 h
25   to CO concentrations of 50 and 100 ppm, which resulted in average COHb levels of 2.9% and 4.5%,
26   respectively. Both exposures significantly decreased the time to onset of exercise-induced angina relative
27   to room air control (1.6% COHb). However, there was no difference in response between the two
28   exposure concentrations of CO. In a much larger study, 63 adults with stable angina were exposed for 1 h
29   to two concentrations of CO (average exposure concentrations of 117 and 253 ppm) resulting in average

1   pre-exercise COHb levels of 2.4% and 4.7% (Allred et al., 1989). Relative to control (average COHb

2   0.7%), COHb levels of 2.4% and 4.7% were observed to decrease the time to onset of angina by 4.2% (p

3   = 0.054) and 7.1% (p = 0.004), respectively. In addition, these investigators reported a statistically

4   significant decrease in the time to exercise-induced ST-segment depression with increasing COHb levels.

5   These findings provide some evidence of a significant C-R relationship at COHb concentrations between

6   2.4 and 4.7%. However, the human clinical literature has yet to evaluate the C-R relationship at lower CO

7   concentrations or COHb levels.

8   One study in the epidemiologic literature attempted to examine the C-R relationship at the low end

9   of CO concentrations through a threshold analysis. Samoli et al. (2007) in their examination of the

10   association between short-term exposure to CO and mortality conducted an ancillary analysis to examine

11   the potential presence of a CO threshold. In this analysis the authors compared city-specific models to the

12   threshold model, which consisted of thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007)

13   then computed the deviance between the two models and summed the deviances for a given threshold

14   over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest

15   threshold examined), the comparison with the linear no-threshold model indicated weak evidence (p-

16   value >0.9) for a threshold. However, determining the presence of a threshold at the very low range of CO

17   concentrations (i.e., at 0.43 ppm) in this data set is challenging, because, in seven of the 19 European

18   cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m^3 (1.74 ppm). By only

19   using the 12 cities in the analysis that had minimum CO concentrations approaching 0.5 mg/m^3

20   (0.43 ppm), a limited number of observations were examined around the threshold of interest, which

21   subsequently contributed to the inability to draw conclusions regarding the potential presence of a

22   threshold with any certainty.

2.4.2. Potentially Susceptible and Vulnerable Subpopulations

23   The examination of both susceptible and vulnerable subpopulations to CO exposure allows for the

24   NAAQS to provide an adequate margin of safety for both the general population and sensitive

25   subpopulations (see Section 5.7 for a more detailed discussion). During the evaluation of the CO

26   literature, numerous studies were identified that examined whether underlying factors increased the

27   susceptibility or vulnerability of an individual to CO-related health effects. In this ISA, a susceptible

28   subpopulation is defined as those individuals with intrinsic biological characteristics that might exhibit an

29   adverse health effect to a pollutant at concentrations lower than those needed to elicit the same response

30   in the general population or those individuals that might elicit a more adverse health effect at the same

31   concentration. A vulnerable subpopulation is defined as those individuals with external, nonbiological

32   factors that increase the risk of adverse health effects, such as differential exposure or living at altitude.

1   The most important susceptibility characteristic for increased risk due to CO exposure is CAD.

2   Individuals with heart disease may be at a greater risk from CO exposure since they may already have

3   compromised O_2 delivery. CO is notable among air pollutants because it is especially harmful in

4   individuals with impaired cardiovascular systems. Persons with a normal cardiovascular system can

5   tolerate substantial concentrations of CO, if they vasodilate in response to the hypoxemia produced by

6   CO. In contrast, individuals unable to vasodilate in response to CO exposure may show evidence of

7   ischemia at low concentrations of COHb. Many of the controlled human exposure studies have focused

8   on individuals with IHD. Other medical conditions that confer increased susceptibility include obstructive

9   lung disease, which impairs airflow to the lungs, and conditions such as anemia that alter the blood O_2

10   carrying capacity or content and result in a greater risk from COHb induced hypoxia and decreased tissue

11   O_2 delivery. Age is important for susceptibility in older adults, who have an increased elimination time for

12   COHb. Newborns can also be considered a susceptible subpopulation due to critical phases of

13   development and differences between fetal and maternal CO pharmacokinetics in utero.

14   Subpopulations considered vulnerable to CO-related health effects include people who spend a

15   considerable amount of time in or near traffic, live at high altitude, exercise and/or use medications which

16   may increase endogenous CO production. Individuals that spend a substantial amount of time on or near

17   heavily traveled roadways, such as commuters and those living or working near freeways, are likely to

18   experience elevated CO concentrations and therefore constitute a potentially vulnerable subpopulation

19   due to differential exposure. Vulnerable subpopulations also include individuals at high altitude, who

20   undergo physiologic changes that favor increased CO uptake and COHb formation. Exercising

21   individuals are also considered vulnerable because exercise facilitates CO uptake and transport by

22   increasing gas exchange efficiency and the COHb elimination rate decreases with physical activity.

23   Individuals who use certain medications which may increase endogenous CO production and the baseline

24   level of COHb are also considered vulnerable to CO-related health effects.

Chapter 3. Source to Exposure

3.1. Introduction

1   This chapter contains basic information about concepts and findings in atmospheric sciences and
2   exposure assessment pertaining to CO levels relevant for establishing a foundation for the detailed
3   discussions of health effects data in subsequent chapters. Section 3.2 provides an overview of the sources
4   of CO and examples of their spatial distribution. Atmospheric chemistry involved in the production and
5   removal of CO by oxidation processes is discussed in Section 3.3. Descriptions of CO measurement
6   methods and monitor siting requirements and locations are presented in Section 3.4. Data for ambient CO
7   concentrations are characterized in Section 3.5. Policy relevant background concentrations of CO,
8   i.e., those concentrations defined to result from uncontrollable emissions, are also presented in Section
9   3.5. Finally, factors related to human exposure to CO are discussed in Section 3.6.

3.2. Sources and Emissions of CO

10   CO is a colorless, odorless, tasteless gas consisting of one carbon (C) atom covalently bonded to
11   one O_2 atom; its molar mass is 28.0101 g/mol. CO is formed primarily by incomplete combustion of
12   carbon-containing fuels and photochemical reactions in the atmosphere. In general, any increase in fuel
13   O_2 content, burn temperature, or mixing time in the combustion zone will tend to decrease production of
14   CO relative to CO_2; hence CO emissions from large fossil-fueled power plants are typically very low
15   since the boilers at these plants are tuned for highly efficient combustion with the lowest possible fuel
16   consumption. Internal combustion engines used in mobile sources, by contrast, have widely varying
17   operating conditions and, thus, inherently higher and varying CO formation.
18   Figure 3-1 lists CO emissions totals in tons segregated by individual source sectors in the U.S. for
19   2002, which is the most recent publicly available data. In the U.S., CO emissions data are tracked in the
20   National Emissions Inventory (U.S. EPA, 2006a), a composite of data from various sources including
21   industries and state, tribal, and local air agencies. NEI data are collected for all states, the District of
22   Columbia, the U.S. territories of Puerto Rico and Virgin Islands, and some of the territories of federally
23   recognized American Indian nations. Different data sources use different data collection methods, most of
24   which are based on engineering calculations and estimates rather than measurements. Most fuel
25   combustion and industrial sources, for example, estimate their CO emissions using EPA-approved
26   emission factors, as do on-road and non-road mobile source emitters (U.S. EPA, 2007). Although these

1 estimates are generated using well-established approaches, uncertainties are inherent in the emission

2 factors and models used to represent sources for which emissions have not been directly measured.

3 Nationally, on-road mobile sources in the NEI constituted more than half of total CO emissions in

4 2002, or ~63 MT of ~109 MT total. For this reason, high concentrations of CO can often occur in areas of

5 heavy traffic. In metropolitan areas in the U.S., for example, as much as 70-75% of all CO emissions

6 came from on-road vehicle exhaust in the 2002 NEI (U.S. EPA, 2006a). The majority of these on-road CO

7 emissions derive from gasoline-powered vehicles since the O_2 content, pressure, and temperature required

8 for diesel fuel ignition result in much less CO production. When the emissions from incomplete

9 combustion of fuels powering non-road mobile sources were included, all mobile sources accounted for

10 ~80% of total CO emissions in the U.S. in 2002; see Figure 3-1.

Nationwide Emissions 2002
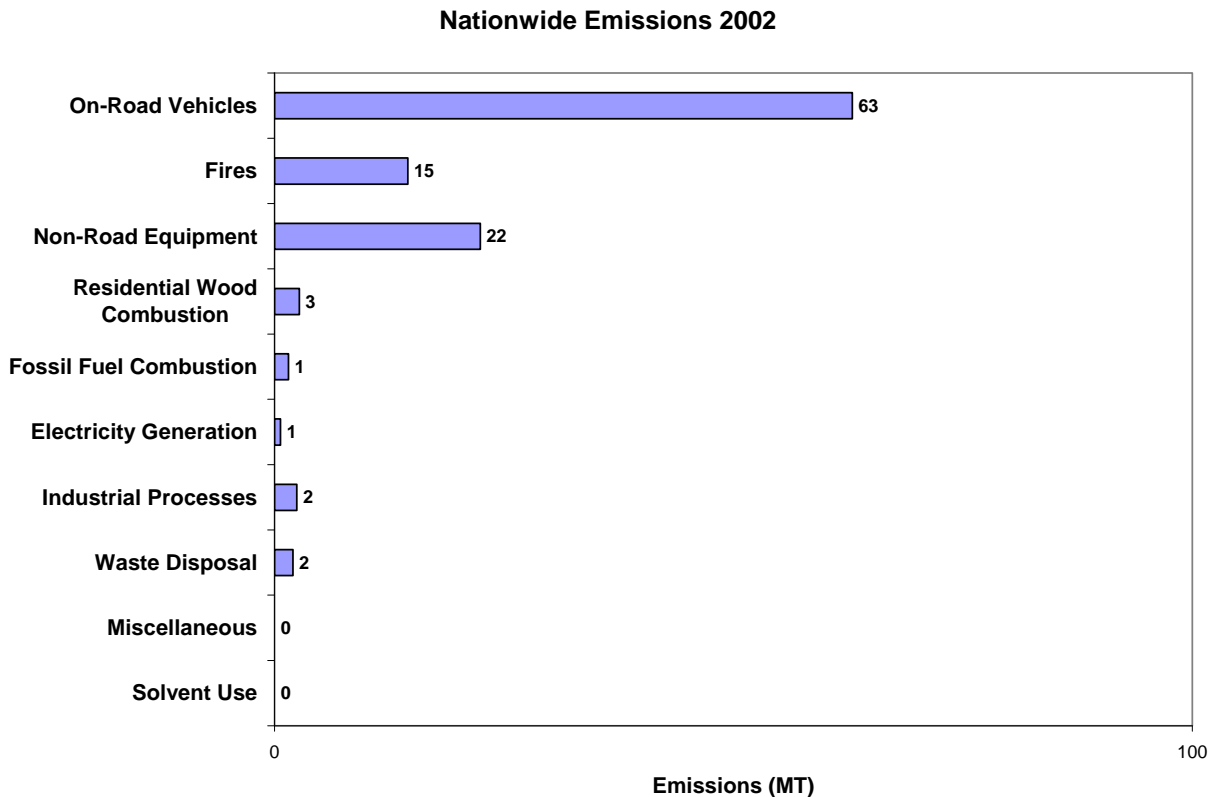
Source: U.S. EPA (2006a)

Figure 3-1.   CO emissions (MT) in the U.S. by source sector in 2002.

11 Figure 3-2 shows present and historical CO emissions from the traditionally inventoried

12 anthropogenic source categories: (1) fuel combustion, which includes emissions from coal-, gas-, and oil-

13 fired power plants and industrial, commercial, and institutional sources, as well as residential heaters

14 (e.g., wood-burning stoves) and boilers; (2) industrial processes, which includes chemical production,

1 petroleum refining, metals production, and industrial processes other than fuel combustion; (3) on-road

2 vehicles, which includes cars, trucks, buses, and motorcycles; and (4) non-road vehicles and engines, such

3 as farm and construction equipment, lawnmowers, chainsaws, boats, ships, snowmobiles, aircraft,

4 locomotive, and others. Using these NEI data, trends in the national CO emissions can be computed and

5 compared over time. So, for example, the national-scale estimated anthropogenic CO emissions decreased

6 35% between 1990 and 2002; see Figure 3-2. The trend plot in Figure 3-2 demonstrates that controls in

7 the on-road vehicle sector have produced nearly all the national-level CO reductions since 1990. Data are

8 presented here for 1990 and from 1996 to 2002 because only the 1990 data has been updated to be

9 comparable to the more recent inventories made since 1996.
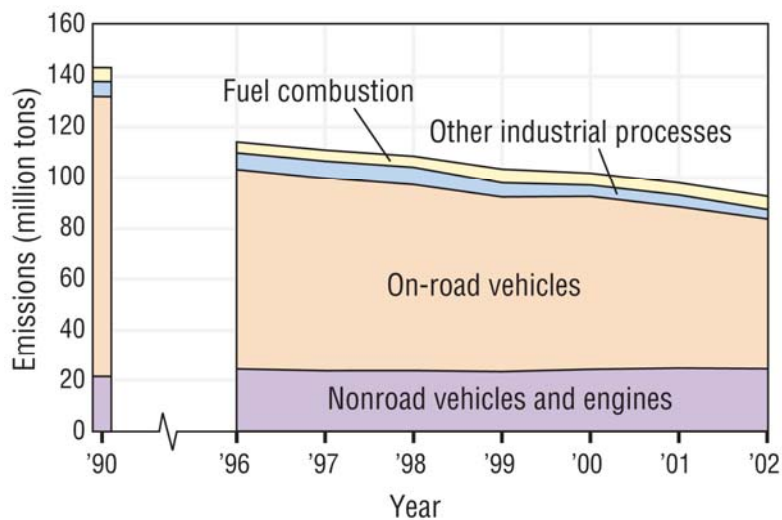
Source: U.S. EPA (2006a, 2008c)

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

10   With the exception of this downward trend resulting from emissions controls, anthropogenic CO

11 emissions demonstrate less interannual variability than biogenic emissions (Bergamaschi et al., 2000).

12 Several recent reports using both ambient concentrations and fuel-based emissions estimates have

13 explored this annual-to-decadal emissions decrease in anthropogenic CO in finer detail. They included

14 Harley et al. (2001; 2005), Parrish et al. (2002; 2006), Pollack et al. (2004), and Mobley et al. (2005). The

15 consistent conclusion from those investigations has been that annual average U.S. on-road vehicle CO

16 emissions decreased at a rate of ~5% per year since the early 1990s. Additional analyses by Harley et al.

17 (2005), Parrish et al. (2002) and Parrish (2006) were also consistent with the suggestion in Pollack et al.

18 (2004) that the EPA MOBILE6 vehicle emissions model (http://www.epa.gov/otaq/m6.htm) now

19 overestimates vehicle CO emissions by a factor of ~2.

1   Biogenic emissions can vary widely from year to year (Bergamaschi et al., 2000). CO isotopes,
2   most notably ^{14}CO, have been especially useful in helping refine emissions estimates and partition them
3   between combustion and other sources. Weinstock and Niki (1972) analyzed measurements of the ^{14}C
4   content of CO in Tonawanda, NY (a suburb of Buffalo) obtained by MacKay et al. (1963) during the
5   winter of 1960 and found at that time that a large proprotion of the CO was produced by sources
6   containing modern carbon and not fossil carbon. The main source of this modern carbon CO was
7   conjectured by Weinstock and Niki (1972) to have been from photochemical oxidation of CH_4; however,
8   CH_4 has a long atmospheric life time (about 8 years) but does oxidize to compounds like methyl radical
9   and also is a contributor to O_3 formation. Other work suggested that CO sources such as isoprene
10   oxidation and biomass burning were also important. For example, Conny (1998) reviewed studies using
11   measurements of ^{14}CO to characterize winter sources of CO in Las Vegas, NV, and Albuquerque, NM.
12   These studies concluded that the contribution from residential wood burning could have been as high as
13   30% in the samples collected.

14   Estimates of non-anthropogenic CO emissions are made using the Biogenic Emissions Inventory
15   System (BEIS) model with data from the Biogenic Emissions Landcover Database (BELD) and annual
16   meteorological data; see http://www.epa.gov/ttnchie1/emch/biogenic. National biogenic emissions,
17   excluding fires, were estimated to contribute ~5% of total CO emissions from all sources in 2002; fires in
18   2002 added another 13%, or ~14.5 MT, to the national CO emissions total. Geogenic emissions of CO
19   also included in this inventory, include volcanic gases released from molten rock in the earth's mantle.
20   Mixing ratios of dissolved CO in this rock vary in a range from 0.01 to 2% as a function of the rock
21   stratum surrounding the volcano and other geologic conditions. This high variability and infrequent
22   though often violent release mean geogenic CO measurements are very difficult to make with precision.
23   On a global scale, however, the magnitude of their contribution is small relative to all anthropogenic
24   sources. Photodecomposition of organic matter in oceans, rivers, lakes, and other surface waters, and
25   from soil surfaces also releases CO (Goldstein and Galbally, 2007). However, soils can act as a CO source
26   or a sink depending on soil moisture, UV flux reaching the soil surface, and soil temperature (Conrad and
27   Seiler, 1985). Soil uptake of CO is driven by anaerobic bacteria (Inman et al., 1971). Emissions of CO
28   from soils appear to occur by abiotic processes, such as thermodecomposition or photodecomposition of
29   organic matter. In general, warm and moist conditions found in most soils favor CO uptake, whereas hot
30   and dry conditions found in deserts and some savannas favor the release of CO (King, 1999).

31   Biomass burning consists of wildfires and the intentional burning of vegetation to clear new land
32   for agriculture and population resettlement; to control the growth of unwanted plants on pasture land; to
33   manage forest resources with prescribed burning; to dispose of agricultural and domestic waste; and as
34   fuel for cooking, heating, and water sterilization. Globally, most wildfires may be ignited directly as the
35   result of human activities leaving only 10 to 30% initiated by lightning (Andreae, 1991). However,
36   because fire management practices suppress natural wildfires, the buildup of fire fuels increases the

1   susceptibility of forests to more severe but less frequent fires in the future. There is considerable

2   uncertainty in attributing the fraction of wildfire emissions to human activities because the emissions

3   from naturally occurring fires that would have been present in the absence of fire suppression practices

4   are not known.

5   Biomass burning also exhibits strong seasonality and interannual variability (van der Werf et al.,

6   2006), with most biomass burned during the local dry season. This is true for both prescribed burns and

7   wildfire. The unusually warm and dry weather in central Alaska and western Yukon in the summer of

8   2004, for example, contributed to the burning of 11 million acres there. These fires, the largest on record

9   for this region, produced CO emissions easily tracked by the Measurement of Pollution in the

10   Troposphere (MOPITT) instrument on NASA's Terra satellite; see Figure 3-3. The high CO concentration

11   measured by MOPITT coincided with the surface location of fires using aerosol plumes identified by the

12   Moderate Resolution Imaging Spectroradiometer (MODIS) also on Terra. Subsequent modeling by Pfister

13   et al. (2005) showed that the CO contribution from these fires in July 2004 was 30 ($\pm$5) teragrams (Tg)

14   that summer, or in the range of the total U.S. anthropogenic CO emissions during the same time.

15   The smoldering phase of combustion yields higher CO emissions than the flaming phase. Using

16   controlled combustion chamber experiments Lobert et al. (1991) found that with a wide variety of

17   vegetation types, on average, 84% of the CO from biomass fires was produced during the smoldering

18   phase and 16% during the flaming phase of combustion.

19   CO emissions data for EPA's ten administrative Regions in the U.S. depicted in Figure 3-4 show a

20   more nuanced view of the national concentrations and trends described just above. Net anthropogenic CO

21   emissions were estimated to have declined in all EPA Regions between 1990 and 2002 with the largest

22   decrease (10.8 MT) occurring in Region 9.

23   On still finer scales, CO emissions from on-road mobile sources or from fires can dominate in

24   different places across the U.S. Figure 3-5 illustrates this variability with CO state-level emissions total

25   and selected county totals in 2002 for Colorado. (Annex A includes analogous data for Alaska, Utah,

26   Massachusetts, Georgia, California, and Alabama.) In Colorado, emissions from fires and on-road

27   vehicles were nearly equal: ~0.9 MT from fires and ~1.1 MT from on-road vehicles, though emissions

28   varied strongly across counties with urban Denver County dominated by on-road vehicle emissions at

29   71% and rural Garfield County dominated by fire emissions at 67%.
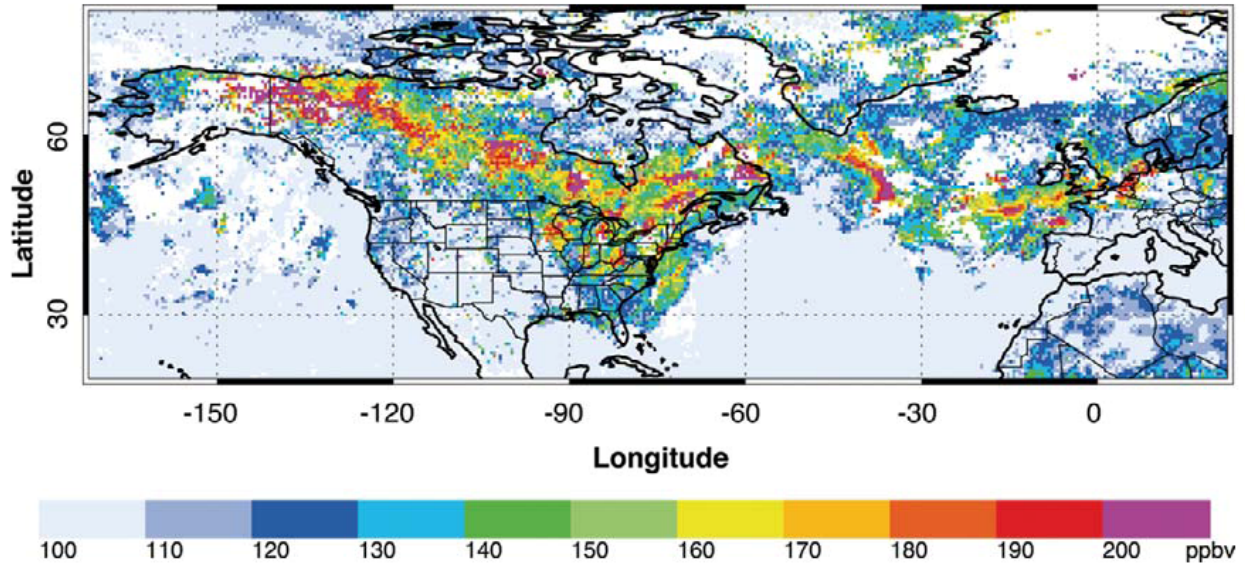
Source: Fishman et al. (2008)

Figure 3-3. CO concentrations measured by satellite at the 700 hectoPascal level (~10,000 feet above sea level) from MOPITT for the period 15-23 July 2004 during intense wildfires in Alaska and Yukon.
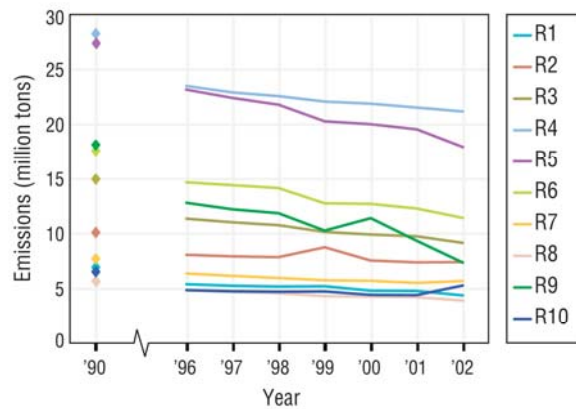
Data are presented for 1990 and 1996-2002, as datasets from these inventory years are all fully up to date. Data are available for inventory years 1991-1995, but these data have not been updated to allow comparison with data from 1990 and 1996-2002.

Source: U.S. EPA (2006a, 2008c)

Figure 3-4. Trends in sub-national CO emissions in the 10 U.S. EPA Regions for 1990 and 1996 to 2002.
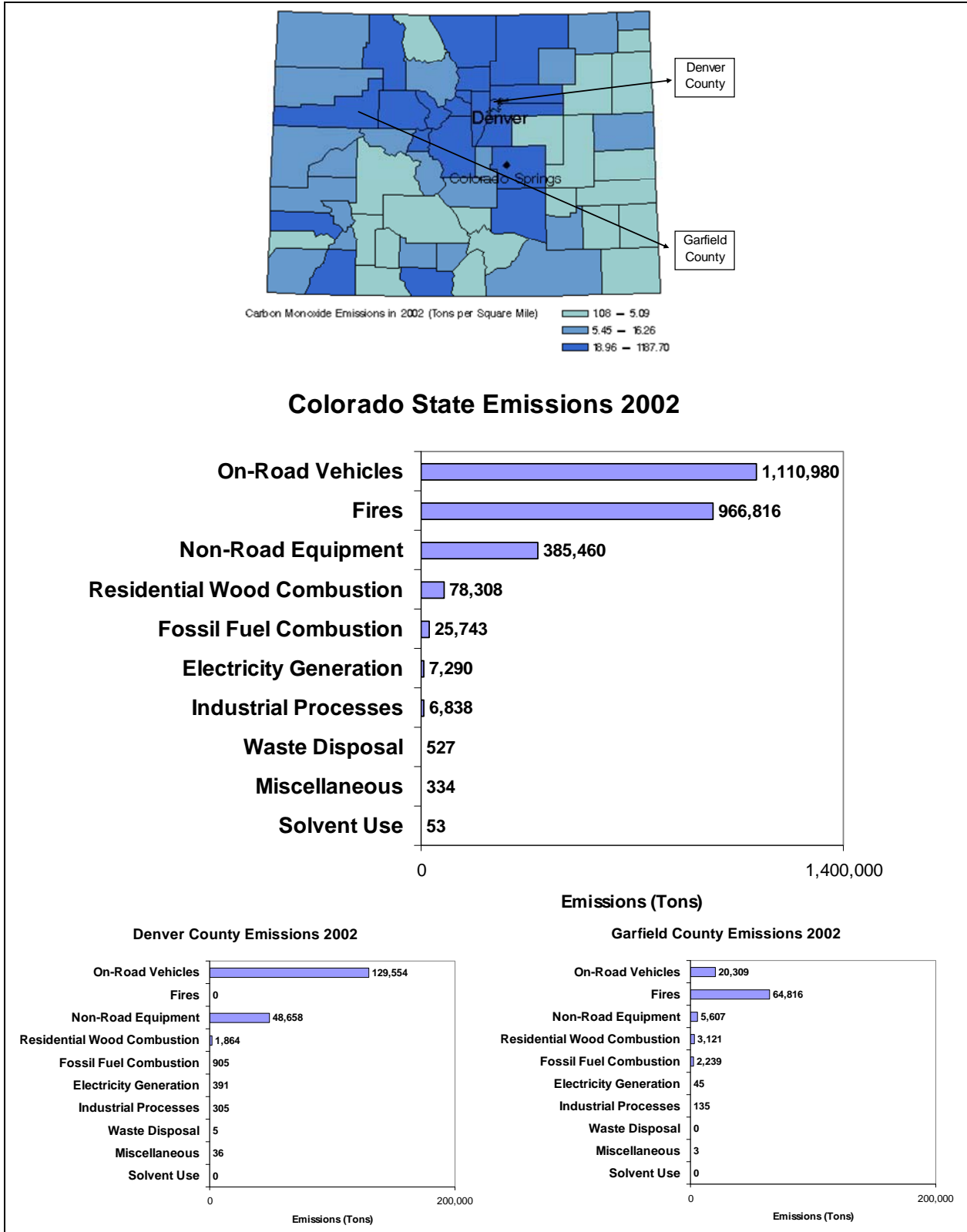
Figure 3-5. CO emissions density map and distribution for the state of Colorado, and for selected counties in Colorado.

3.3. Physics and Chemistry of Atmospheric CO

1   In addition to being emitted directly by combustion sources, CO is produced by photooxidation of
2   methane (CH_4) and other VOCs including nonmethane hydrocarbons (NMHCs) in the atmosphere, and of
3   organic molecules in surface waters and soils. CH_4 oxidation is summarized in the following reaction
4   sequence:

$$CH_4 + OH \rightarrow CH_3 + H_2O$$
$$CH_3 + O_2(+M) \rightarrow CH_3O_2(+M)$$
$$CH_3O_2 + NO \rightarrow CH_3O + NO_2$$
$$CH_3O + O_2 \rightarrow CH_2O + HO_2$$
$$CH_2O + h\nu \rightarrow H_2 + CO$$
$$or \quad CH_2O + h\nu \rightarrow HCO + H$$
$$or \quad CH_2O + OH \rightarrow HCO + H_2O$$
$$HCO + O_2 \rightarrow CO + HO_2$$
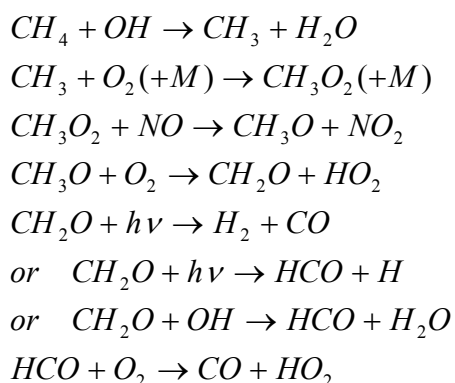
5   where M is a reaction mediator providing collisional energy but is neither created nor destroyed.
6   Photolysis of formaldehyde (CH_2O) proceeds by two pathways. The first produces molecular
7   hydrogen (H_2) and CO with a reaction yield of 55% in conditions of clear skies and low zenith angles; the
8   second yields a hydrogen radical (H) and the formyl radical (HCO). HCO then reacts with O_2 to form
9   hydroperoxy radical (HO_2) and CO. Reaction of methyl peroxy radical (CH_3O_2) with HO_2 radicals
10   (reaction not shown) to form methyl hydroperoxide (CH_3OOH) is also operative, especially in low oxides
11   of nitrogen (NO_X) conditions. Heterogeneous removal of the water-soluble intermediate products
12   CH_3OOH, CH_2O, and radicals will decrease CO yields from CH_4 oxidation.
13   While oxidation of CH_2O nearly always produces CO and some small quantities of formic acid
14   (CH_2O_2) in the reaction of CH_2O with HO_2 (not shown here), oxidation of acetaldehyde (CH_3CHO) does
15   not always yield two CO molecules. Reaction of CH_3CHO with OH can yield acetyl radicals (CH_3CO)
16   which then will participate with O_2 in a termolecular recombination reaction to form peroxyacyl radicals,
17   which then can react with nitric oxide (NO) to form CH_3 and CO_2; or the peroxyacyl radicals can react
18   with NO_2 to form peroxyacetyl nitrate (PAN), $CH_3CO_3NO_2$. In this way, one carbon atom is oxidized
19   directly to CO_2 without passing through CO. The yield of CO from these pathways depends on the OH
20   concentration and the photolysis rate of CH_3CHO, as well as on the abundance of NO, since peroxyacyl
21   radicals also will react with other odd hydrogen radicals like OH.
22   Estimating the CO yield from oxidation of hydrocarbons (HCs) larger than CH_4 requires computing
23   the yields of CH_2O, CH_3CHO, CH_3CO, and analogous radicals from oxidation of the parent molecules.
24   Moreover, the extent of heterogeneous removal of soluble intermediate products also affects oxidation of
25   more complex HCs. However, the detailed gas-phase kinetics for many HCs with more than a few

1   carbons is still unknown, and this is especially the case for several important classes of VOCs including

2   the aromatics, biogenic HCs including isoprene, and their intermediate oxidation products like epoxides,

3   nitrates, and carbonyls. It has long been known that as much as 30% of the carbon in HCs in many urban

4   areas is in the form of aromatics largely from mobile sources since gasoline contains significant quantities

5   of aromatics (Grosjean and Fung, 1984; Seila et al., 1989). Yet mass balance analyses performed on

6   irradiated smog chamber mixtures of aromatic HCs indicate that only about one-half of the carbon is in

7   the form of compounds that can be identified. In addition, reactions like the oxidation of terpenes that

8   produce condensable products are also significant because these reactions produce secondary organic

9   aerosols, thereby reducing the potential yield of CO. The CO yield from oxidation of CH_4, for example, is

10   ~0.9 on a per carbon basis (Kanakidou and Crutzen, 1999). Yields from other compounds range from less

11   than 0.1 for anthropogenic alkanes (Altshuller, 1991) to ~0.7 for some other non-CH_4 HCs; see

12   Kanakidou and Crutzen (1999) for CO yields from other HCs.

13   The major pathway for removal of CO from the atmosphere is reaction with OH to produce CO_2

14   and H radicals that rapidly combine with O_2 to form HO_2 radicals with a rate constant at 1 atm in air of

15   ~2.4×10^{-13} cm^3/molecule/s (Finlayson-Pitts and Pitts Jr). The mean tropospheric photochemical lifetime

16   (τ) of CO in the northern hemisphere is ~57 days (Khalil and Rasmussen, 1990; Thompson and Cicerone,

17   1986). Owing to variation in atmospheric water vapor, OH concentration, and insolation, shorter τ are

18   found nearer the tropics and longer ones at higher latitudes. During winter at high latitudes CO has nearly

19   no photochemical reactivity on urban and regional scales. The CO τ is shorter than the characteristic time

20   scale for mixing between the hemispheres of ~1 year; hence a large gradient in concentrations can exist

21   between the hemispheres. In addition, the CO τ at high latitudes is long enough to result in much smaller

22   gradients between 30° latitude and the pole of either hemisphere. The typical residence times of CO in

23   urban areas when assuming a diel-average OH concentration of 3×10^6/cm^3 in urban areas is ~16 days, so

24   CO will not be destroyed in urban areas where it is emitted and will likely be mixed on continental and

25   larger scales. OH concentrations are orders of magnitude lower in indoor environments and so CO will

26   generally not be destroyed by indoor air reactions.

27   Recent data do not alter the current well-established understanding of the role of urban and regional

28   CO in continental and global-scale chemistry outlined in the 2000 CO AQCD (U.S. EPA, 2000), and

29   subsequently confirmed in the global assessments of climate change by the Intergovernmental Panel on

30   Climate Change (IPCC, 2001, 2007). CO is a weak contributor to greenhouse warming because its

31   fundamental absorption band near 4.63 μm is far from the spectral maximum of earth's longwave

32   radiation at ~10 μm. However, because reaction with CO is also the major sink for OH, changes in CO

33   concentrations can lead to changes in the concentrations of other trace gases whose loss processes involve

34   OH attack. Some of these trace gases, CH_4, for example, absorb infrared radiation from the earth's surface

35   and contribute to the greenhouse effect directly; others, including the hydrochlorofluorocarbons (HCFCs)

1 and methyl chloride and methyl bromide, can deplete stratospheric O_3, increasing the surface-incident UV

2 flux.

3   This indirect effect of CO on stratospheric O_3 concentrations is opposite in sign to the effect of CO

4 on O_3 in the troposphere where CO reacts in a manner similar to other VOCs in the presence of NO_X and

5 UV to create O_3. (See the detailed description of O_3 formation from VOCs and NO_X in the 2008 NO_X ISA

6 (U.S. EPA, 2008e). The long chemical lifetime and one-to-one stoichiometry of CO oxidation (whereby

7 one molecule of CO converts only one molecule of NO to NO_2) means that CO has significantly lower O_3

8 forming potential than other VOCs in the troposphere. Carter (1998) computed a maximum incremental

9 reactivity for CO of 0.07 g O_3 for 1 g CO, as compared to reactivities of total on-road vehicle exhaust

10 emissions in the range of 3 to 4. However, because the total mass of CO emissions is substantially greater

11 than those of the other VOCs with higher carbon numbers and faster reactivities, CO can contribute

12 greatly to O_3 formation even though its photochemical processing is slow. Using data from instrumented

13 models including that of Jeffries (1995), NRC (1999) estimated, for example, that CO can contribute 15-

14 25% of the total O_3 forming potential of gasoline exhaust emissions; this figure varies from region to

15 region. The contribution of CO to urban and regional O_3 concentration is often less than 10% owing to its

16 very slow reactivity on these scales and to locally variable radical concentration ratios.

17   Because the greenhouse warming effects from CO are nearly completely indirect, and because CO

18 concentrations are spatially heterogeneous, neither the IPCC nor EPA computes global warming potentials

19 (GWPs) for CO, just as they do not for tropospheric O_3, NO, NO_2, or VOCs (U.S. EPA, 2008a).

20 Additionally, urban and regional-scale oxidation of CO to CO_2 under current atmospheric conditions

21 proceeds very slowly and IPCC considers production of CO_2 through this pathway to be double counting

22 of CO effects (IPCC, 2007).

3.4. Ambient Measurements

3.4.1. Ambient Measurement Instruments

23   To promote uniform enforcement of the air quality standards set forth under the Clean Air Act, EPA

24 has established provisions in the Code of Federal Regulations (CFR) under which analytical methods can

25 be designated as federal reference methods or federal equivalent methods (FRM or FEM, respectively).

26 Measurements for determinations of NAAQS compliance must be made with FRMs or FEMs. As of

27 December 2008, 19 automated FRMs and no FEMs had been approved for CO

28 (http://www.epa.gov/ttn/amtic/criteria.html).

1   All EPA FRMs for CO operate on the principle of nondispersive infrared (NDIR) detection and can

2   include the gas filter correlation (GFC) methodology. NDIR is an automated and continuous method

3   based on the specific absorption of infrared radiation by the CO molecule. Most commercially available

4   analyzers incorporate a gas filter to minimize interferences from other gases and operate near atmospheric

5   pressure. The most sensitive trace-level versions of these instruments can detect minimum CO

6   concentrations of ~0.04 ppm; the required lower detection limit for FRMs in the EPA network is 1.0 ppm

7   (40 CFR 53.20 Table B-1).

8   NDIR is based on the physics of CO's characteristic infrared absorption near 4.63 μm. NDIR

9   methods have several practical advantages over other techniques for CO detection in that they are not

10 sensitive to flow rate changes, require no wet chemicals, are reasonably independent of ambient air

11 temperature changes, are sensitive over wide concentration ranges, and have fast response times. Earlier

12 concerns over zero-drift and nonlinear span responses have been addressed. An extensive and

13 comprehensive review of NDIR, GFC, and alternative, non-FRM techniques for CO detection including

14 tunable diode laser spectroscopy, gas chromatography, mercury liberation, and resonance fluorescence

15 was made for the 2000 CO AQCD (U.S. EPA, 2000), and the reader is directed there for additional

16 information. The description here is limited to a brief outline of the FRM NDIR and GFC techniques.

17   GFC spectroscopy analyzers are used most frequently now in documenting compliance with

18 ambient air standards. A GFC monitor has all of the advantages of an NDIR instrument and the additional

19 advantages of smaller size, no interference from CO_2, and very small interference from water vapor.

20 During operation, air flows continuously through a sample cell. Radiation from the infrared source is

21 directed by optical transfer elements through two main optical subsystems: (1) the rotating gas filter and

22 (2) the optical multipass (sample) cell. The beam exits the sample cell through an interference filter (FC),

23 which limits the spectral passband to a few of the strongest CO absorption lines. Detection of the

24 transmitted radiation occurs at the infrared detector. The gas correlation cell is constructed with two

25 compartments, one filled with 0.5 atm CO, and a second with pure N_2. Radiation transmitted through the

26 CO is completely attenuated at the wavelengths where CO absorbs strongly. The radiation transmitted

27 through the nitrogen gas (N_2) is reduced by coating the exit window of the cell with a neutral attenuator

28 so that the amounts of radiation transmitted by the two cells are made approximately equal in the

29 passband that reaches the detector. In operation, radiation passes alternately through the two cells as they

30 are rotated to establish a signal modulation frequency. If CO is present in the sample, the radiation

31 transmitted through the CO is not appreciably changed, whereas that through the N_2 cell is changed. This

32 imbalance is linearly related to CO concentrations in ambient air.

3.4.2. Ambient Sampling Network Design

3.4.2.1. Monitor Siting Requirements

1   CO monitoring is included at all active NCore sites and State and Local Air Monitoring Stations
2   (SLAMS) where continued measurements of CO using FRM are required until discontinuation is
3   approved by the EPA Regional Administrator. Where SLAMS CO monitoring is required, at least one of
4   the sites must be a max concentration site for that specific area. In 2007, there were ~385 CO monitors
5   reporting values to the EPA Air Quality System (AQS) database. Where CO monitoring is ongoing, 40
6   CFR Part 58 requires at least one CO monitor to capture maximum levels in a given region. This is often
7   done with a monitor situated at the CFR-defined microscale distance (2-10 m) from the side of a roadway
8   for CO. Microscale monitor locations also have sample inlets mounted at 3 ± 0.5 m above ground level,
9   unlike the monitors sampling for larger scales, whose inlet heights can vary between 2 and 15 m. For the
10   CFR-defined middle (up to 500 m) and neighborhood (~500 m-4 km) scale monitoring, the minimum
11   monitor distance from a major roadway is inversely related to the average daily traffic counts on that
12   roadway to ensure that measurements are not substantially influenced by any one roadway. For example,
13   the minimum distance of a middle scale CO monitor from a roadway with an average daily traffic count
14   of 50,000 vehicles per day is 135 m. More detail on siting requirements can be found in 40 CFR Part 58
15   Appendices D through E.

3.4.2.2. Spatial and Temporal Coverage

16   Figure 3-6 depicts the distribution of the ~385 regulatory CO monitors operating in the U.S. in
17   2007. Data from 285 of the ~385 CO monitors operating year-round in the years 2005-2007 met the 75%
18   data completeness criterion for inclusion in the multi-year ambient data analyses for this assessment. The
19   greatest density of monitors is in the CSAs for Los Angeles, CA and San Francisco, CA, and along the
20   Mid-Atlantic sea board. Monitors are also located in regions where biomass burning is more prevalent,
21   such as Anchorage, AK, but not all of these monitors report values from all seasons of all years.
22   Eleven metropolitan regions were chosen for closer investigation of monitor siting based on their
23   relevance to the health studies assessed in subsequent chapters of this ISA and to demonstrate specific
24   points about geospatial distributions of CO emissions and concentrations. These regions were: Anchorage,
25   AK; Atlanta, GA; Boston, MA; Denver, CO; Houston, TX; Los Angeles, CA; New York City, NY;
26   Phoenix, AZ; Pittsburgh, PA; Seattle, WA; and St. Louis, MO. Core-Based Statistical Areas (CBSAs) and
27   Combined Statistical Areas (CSAs), as defined by the U.S. Census Bureau (http://www.census/gov/),
28   were used to determine which counties, and hence which monitors, to include for each metropolitan

1   region.[1] As an example, Figures 3-7 through 3-10 display CO monitor density with respect to population

2   density (for total population and elderly adults aged 65 and over) for Phoenix and Pittsburgh. (Annex A

3   includes analogous plots for the other nine metropolitan regions.)

4   Although ambient monitors for CO and other criteria pollutants are explicitly not located in order

5   to monitor population exposures, it is instructive to test the utility of the current network for

6   characterizing this exposure. Tables 3-1 and 3-2 show the population density around CO monitors for the

7   total population and for elderly adults aged 65 and over for each CSA/CBSA. The percentage of

8   population within specific radii of the monitors for each city was, for the most part, similar between the

9   total and elderly populations. In the cases of Anchorage, Denver, Phoenix, and St. Louis however, the

10   percentage of the elderly population within given radii of the monitors was considerably different

11   compared with the total population. Between-city disparities in population density were larger. Los

12   Angeles, with 85%, and Denver, with 68%, had the largest proportion of the total population within 15

13   km of a monitor. Seattle, with 18%, had the lowest population coverage in large part because ambient CO

14   concentrations there require only a single CO monitor. As concerns the elderly population, Los Angeles,

15   at 83%, Anchorage, at 73%, and Denver, at 70%, had the greatest population coverage within 15 km of a

16   monitor, whereas Seattle, at 18%, again, had the lowest coverage. Proximity to monitoring stations is

17   considered further in sections 3.5 and 3.6 regarding spatial variability within cities. Figures 3-7 through 3-

18   10 show that multiple CO monitors in Phoenix and Pittsburgh were in the city center, and that Pittsburgh

19   also had monitors in outlying areas of moderate to low population density. The CO monitors in Phoenix

20   appear to provide good coverage of areas of the highest total population density, while areas of high

21   elderly population density were located at greater distances from the monitors. CO monitors in Pittsburgh

22   appear to sample areas of high population density well for both the total and elderly populations.

23   Figures 3-13 and 3-15 in section 3.5 and additional figures in Annex A show the locations of CO

24   monitors for the 11 CSAs/CBSAs in relation to major roadways, including Interstate highways, U.S.

25   highways, state highways, and other major roadways required for traffic network connectivity. In most

26   cases, the monitors were concentrated near the center of the CSA/CBSA. Regional background sites were

27   not included on the maps unless they lay within the CSA/CBSA.

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[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.
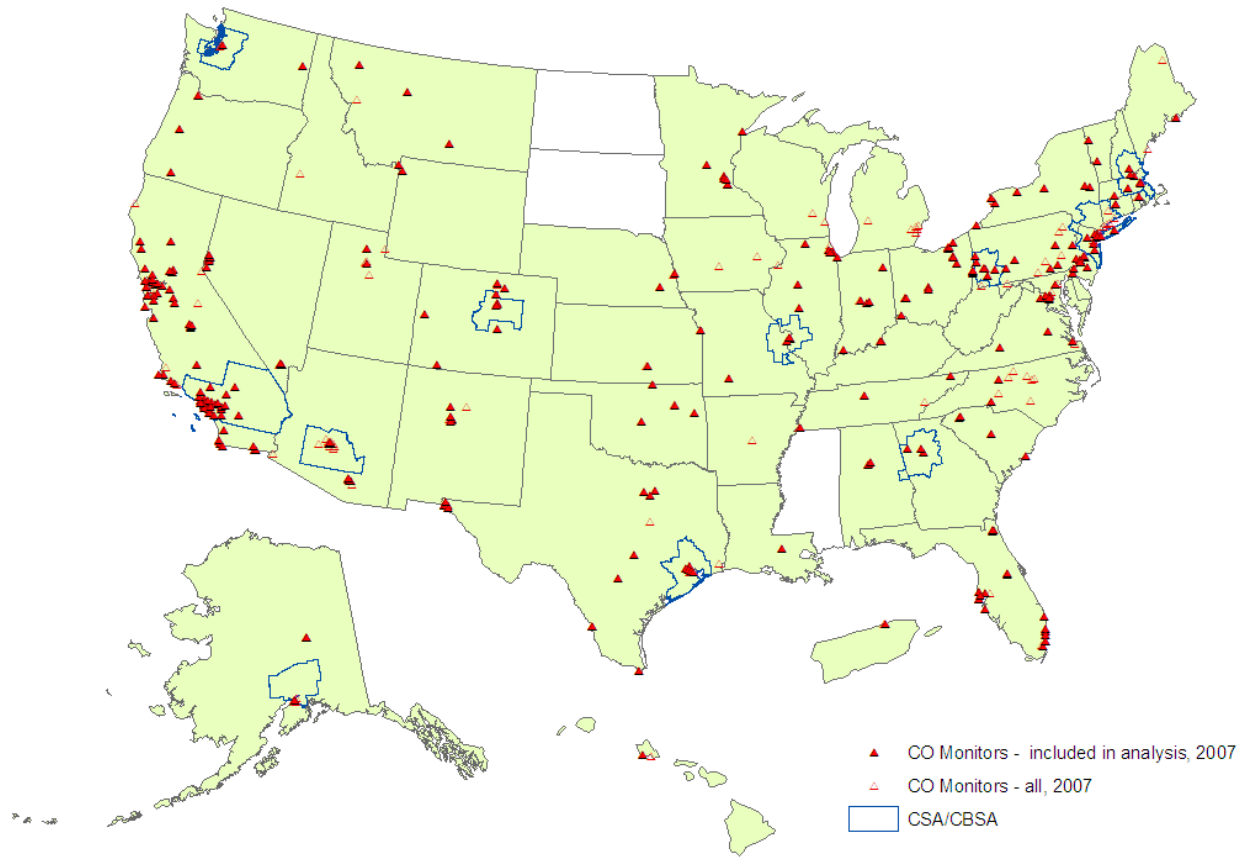
Figure 3-6. Map of ~385 CO monitor locations in the U.S. in 2007. Locations are indicated with triangles: filled triangles show locations of the 285 monitors used in data analysis for this assessment; open triangles are at locations with monitors which did not meet the data completeness requirements for analysis; blue lines mark the boundaries of the 11 CSAs/CBSAs used in the data analysis for this assessment.

Legend (on map):
- CO Monitors - included in analysis, 2007
- CO Monitors - all, 2007
- CSA/CBSA

Phoenix Core Based Statisical Area
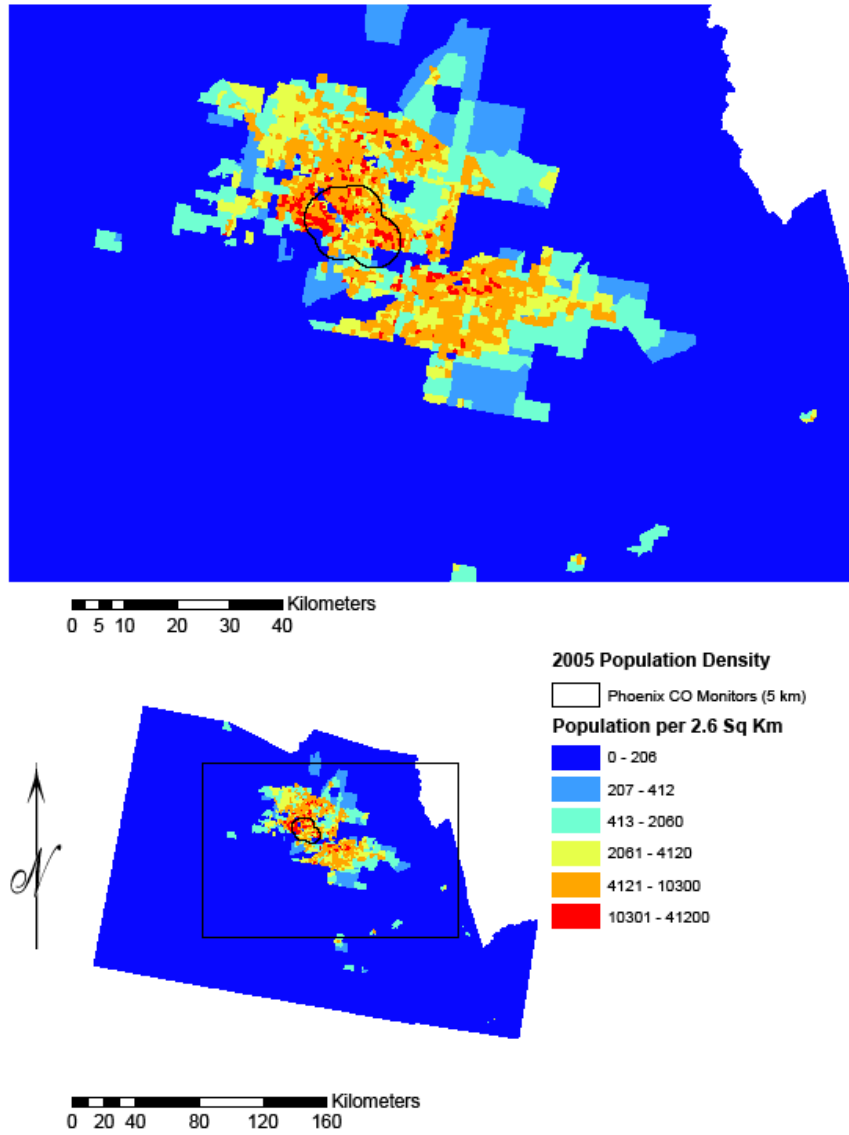
Figure 3-7.   Map of CO monitor locations with respect to population density in the Phoenix, AZ CBSA, total population.
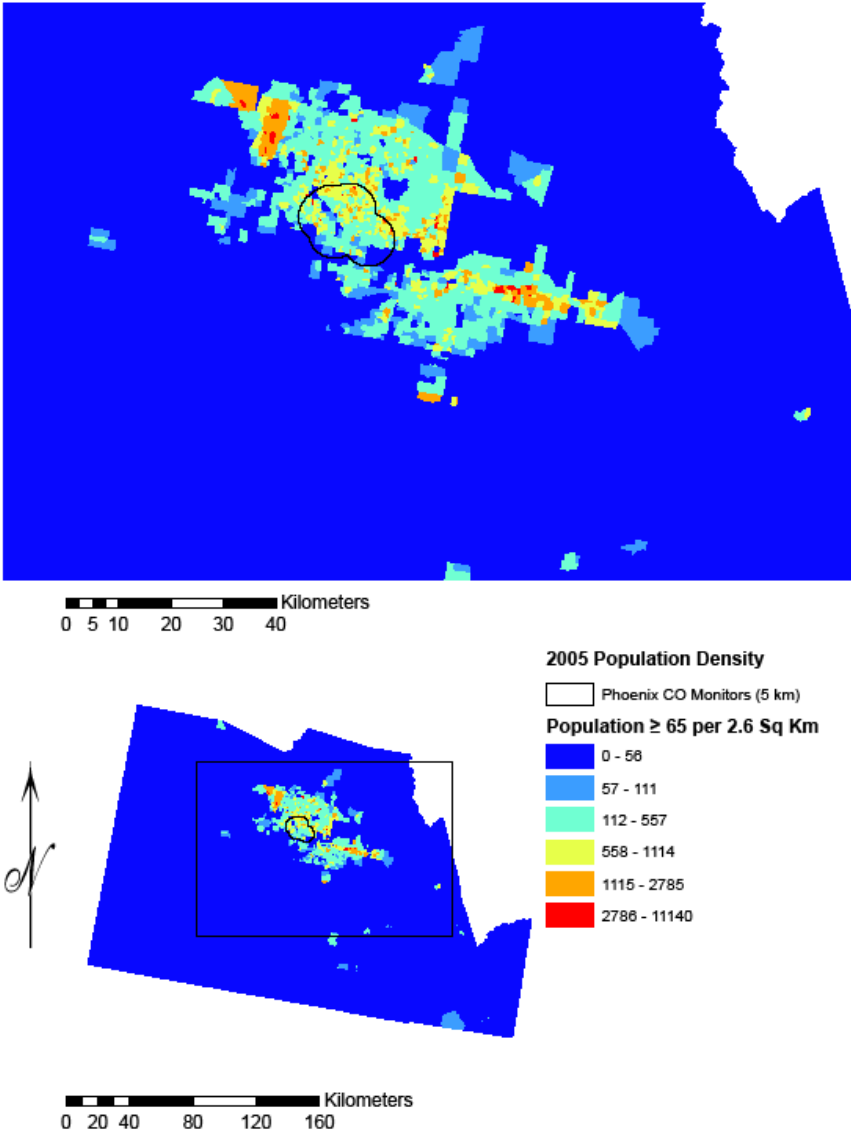
Figure 3-8. Map of CO monitor locations with respect to population density in the Phoenix, AZ CBSA, age 65 and older.

Pittsburgh Combined Statisical Area

Kilometers
0 5 10   20   30   40

2005 Population Density

☐ Pittsburgh CO Monitors (5 km buffer)

Population per 2.6 Sq Km

■	16 - 530
■	531 - 1059
■	1060 - 5296
■	5297 - 10593
■	10594 - 26481
■	26482 - 105925

Kilometers
0 15 30   60   90   120
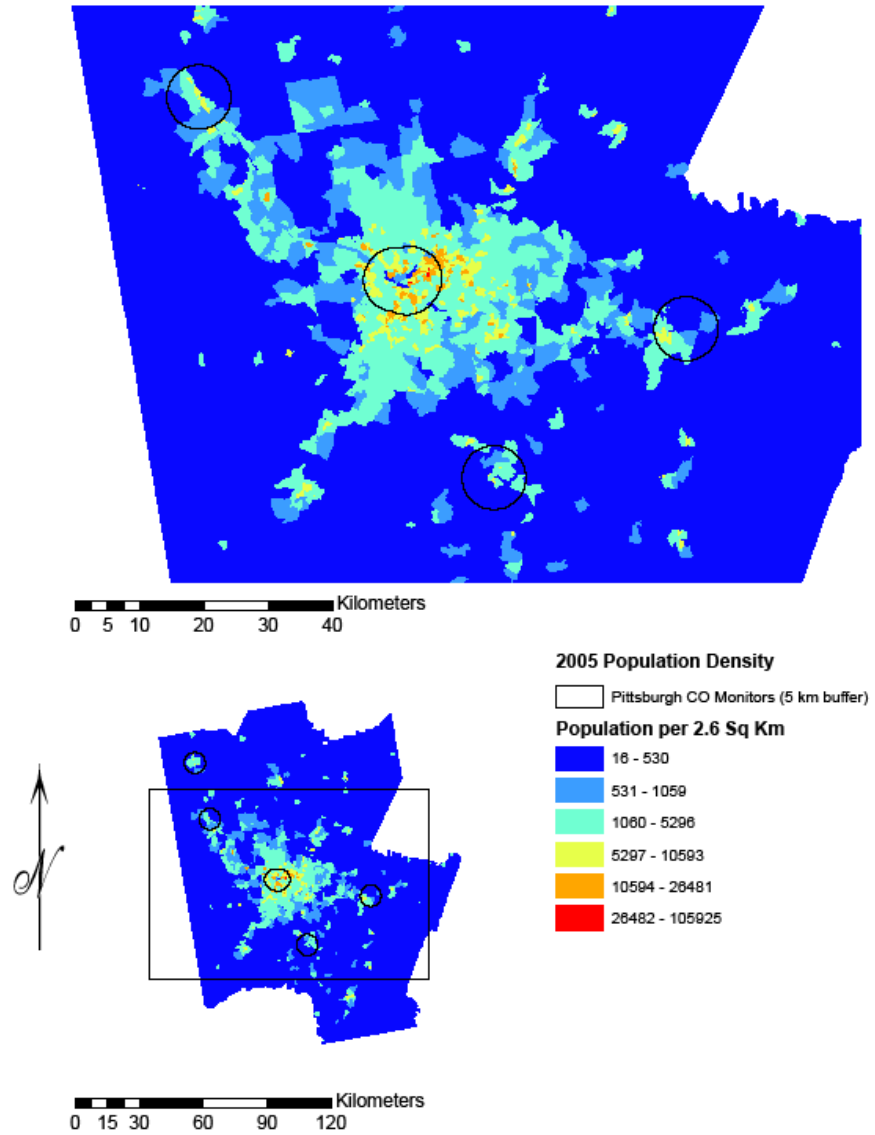
Figure 3-9. **Map of CO monitor locations with respect to population density in the Pittsburgh, PA CSA, total population.**
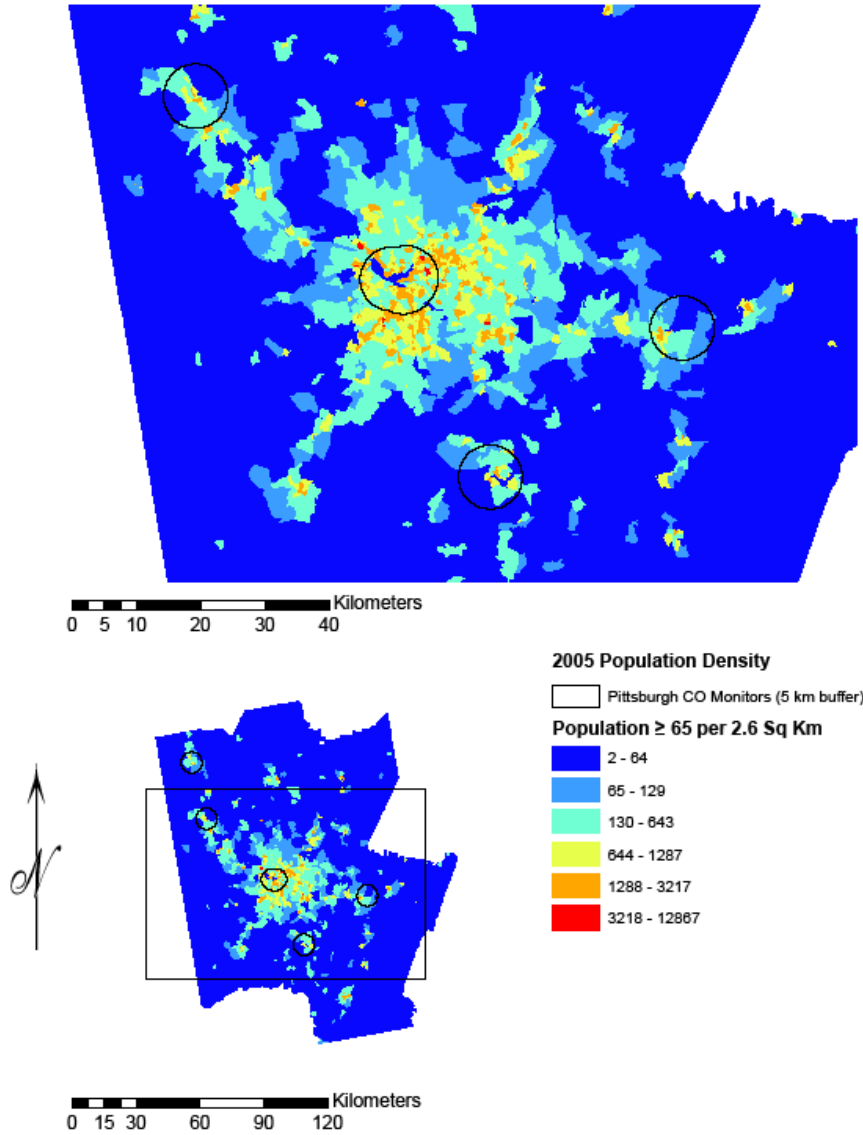
Figure 3-10. Map of CO monitor locations with respect to population density in the Pittsburgh, PA CSA, age 65 and older.

Table 3-1. 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	2,9068	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 3-2. 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	3,1036	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

1   The current NAAQS designates that the level of the NAAQS can only be exceeded once per year at
2   a given location. Figures 3-11 and 3-12 show the second-highest 1-h and second-highest 8-h county-
3   average CO concentrations, respectively, over the U.S. along with estimates of the fraction of U.S. total
4   population exposed to those concentrations. Although 93% of the U.S. counties are not represented in
5   AQS reporting, based on their population densities and proximity to sources, those counties are not
6   expected to have higher concentrations than the ones analyzed here in the absence of extreme events such
7   as wildfires. Continuous hourly averages are reported from U.S. monitoring stations. 1-h and 8-h CO data
8   were available for 243 counties and autonomous cities or municipalities (e.g., Anchorage, AK,
9   Washington, DC) where CO monitors met the 75% data completeness criteria used in this analysis for the
10   years 2005-2007. In 2007, no monitored location reported a second-highest 1-h CO concentration above
11   35 ppm, the level of the current 1-h NAAQS; see Figure 3-11. Moreover, only two monitored locations,
12   one in Weber Co., UT and the other in Jefferson Co., AL (including Birmingham, AL), reported second-
13   highest 1-h CO concentrations above 18 ppm, or approximately one-half the level of the 1-h standard.
14   Figure 3-12 shows that no counties reported second-highest 8-h CO concentrations above 9 ppm, the level
15   of the 8-h NAAQS. Only nine counties reported second-highest 8-h CO concentrations above 4.5 ppm:
16   Jefferson Co., AL, Kay Co., OK, Imperial Co., CA, Weber Co., UT, Philadelphia Co., PA, Anchorage
17   Municipality, AK, Los Angeles Co., CA, Jefferson Co., OH, and San Diego Co., CA.
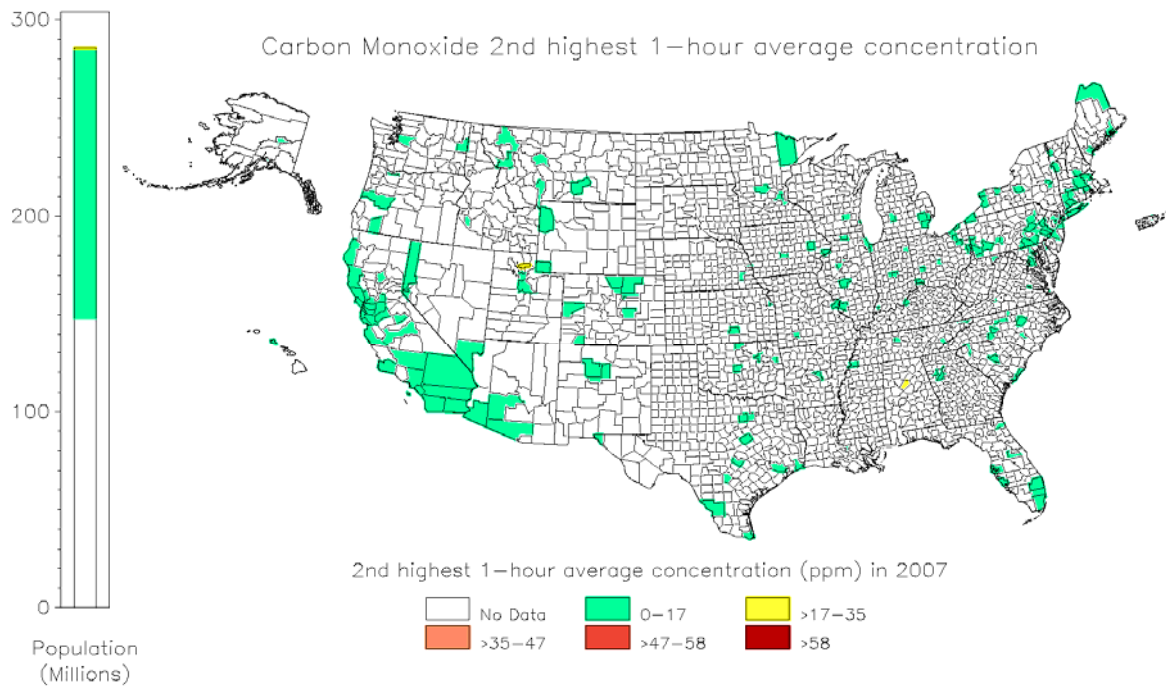
Figure 3-11. County-level map of second-highest 1-h avg CO concentrations in the U.S. in 2007. The bar on the left shows the total U.S. population who live in counties with CO concentrations in the range indicated. Note that approximately 150 million people live in counties with no CO monitors.
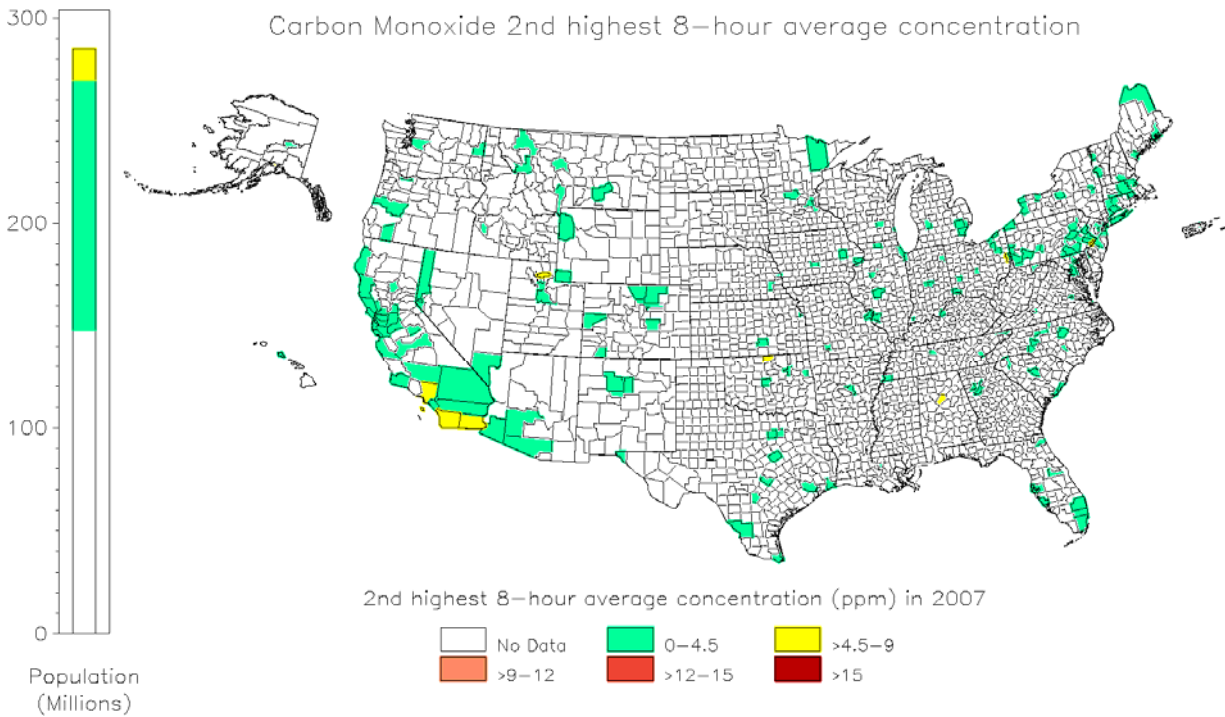
Figure 3-12. County-level map of second-highest 8-h avg CO concentrations in the U.S. in 2007. The bar on the left shows the total U.S. population who live in counties with CO concentrations in the range indicated. Note that approximately 150 million people live in counties with no CO monitors.

Table 3-3. **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 is not available year-round, Anchorage is not included in the nationwide statistics shown in this table.

1 Table 3-3 contains the distribution of hourly CO measurements reported to AQS for 2005-2007. All

2 monitoring locations meeting the 75% data completeness criteria have been included in this table.

3 Anchorage did not meet the data completeness criteria since its monitoring sites were required to report

4 CO measurements during the first and fourth quarters of each year. Anchorage was included in the table,

5 however, for an approximate comparison with the other CSAs and CBSAs reporting year-round

6 measurements to AQS. (Anchorage was not, however, included in the national averages shown in the

1   table.) The nationwide mean, median, and interquartile range for 1-h measurements reported for

2   2005-2007 were 0.5, 0.4 and 0.4 ppm, respectively, and these statistics did not change by more than

3   0.1 ppm over the 3-year period. The largest recorded second-highest 1-h concentration, 26.3 ppm, for this

4   period was reported in 2006 in Birmingham, AL (AQS site ID: 0107360004). The absolute highest 1-h

5   concentration, 39 ppm, between 2005 and 2007, was reported in Ogden, UT (AQS site ID: 490570006).

6   Concentrations are generally highest in the winter (December-February) and fall (September-November)

7   and decrease on average during the spring (March-May) and summer (June-August).

8   Nationwide statistics pooled by site are listed in the center of Table 3-3 and illustrate the

9   distribution of the site average CO concentrations recorded at the 285 monitoring sites for 2005-2007 (see

10   Figure 3-6 for these sites). The site reporting the highest 3-year pooled 1-h avg CO concentration,

11   1.5 ppm, was located in San Juan, Puerto Rico (AQS site ID: 721270003). The eleven individual

12   CSAs/CBSAs discussed earlier are included in the table, none of which reported concentrations above the

13   value of the 1-h NAAQS. Four of the eleven cities (Boston, Houston, Pittsburgh and St. Louis) had 95th

14   percentile 1-h CO concentrations below 1 ppm; the 95th percentile concentrations for the remaining cities

15   were below 3.1 ppm. Lack of year-round monitoring in Anchorage prevented a direct comparison with the

16   other metropolitan regions. However, Anchorage exhibited a 1-h CO distribution shifted higher in

17   concentration when compared to the U.S. average during fall or winter.

Table 3-4.   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	5.1	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

*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.

1   Table 3-4 contains the distribution of 24-h avg CO concentrations derived from the 1-h

2 concentrations reported to AQS and summarized in Table 3-3. The nationwide mean, median, and

3 interquartile range for 24-h avg for 2005-2007 were 0.5, 0.4 and 0.3 ppm, respectively. These were

4 similar to those for the 1-h values. The maximum 24-h avg concentration in these years, 7 ppm, was

5 reported in Birmingham, AL (AQS site ID: 010736004).

Table 3-5.   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

*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.

1   Table 3-5 contains the distribution of 1-h daily max CO concentrations derived from 1-h values

2   reported to AQS for all monitors meeting the inclusion criteria described earlier. The nationwide mean,

3   median, and interquartile range for 1-h daily max concentrations reported for 2005-2007 were 0.9, 0.7 and

4   0.8 ppm, respectively.

Table 3-6.   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.

1   Table 3-6 contains the distribution of 8-h daily max concentrations derived from the 1-h CO

2   concentrations reported to AQS. This was done by first calculating the average concentration for each

3   successive 8-h period, thereby producing 24 8-h avg per day. The maximum of these values for a given

4   monitor within a given day (midnight-to-midnight) was used as the 8-h daily max statistic for that

5   monitor and day. The nationwide mean, median, and interquartile range for 8-h daily max concentrations

1   reported for 2005-2007 were 0.7, 0.5, and 0.5 ppm, respectively. The highest 8-h daily max concentration,

2   10.9 ppm, was recorded at a monitor located five miles north of Newkirk, OK (AQS site ID: 400719010).

3.5.1.2. Urban Scale

3   This section covers urban variability in CO concentrations reported to AQS at the individual

4   CSA/CBSA level. Phoenix, AZ and Pittsburgh, PA were selected for this assessment to illustrate the

5   variability in CO concentrations measured across contrasting metropolitan regions. Information on the

6   other nine cities evaluated for this assessment is included in Appendix A. Maps of the Phoenix CBSA and

7   Pittsburgh CSA shown in Figures 3-13 and 3-15, respectively, illustrate the location of all CO monitors

8   included in the analyses described above. Letters on the maps identify the individual monitor locations

9   and correspond with the letters provided in the accompanying box plots (Figures 3-14 and 3-16) and pair-

10   wise comparison tables (Tables 3-7 and 3-8). The box plots for each monitor include the hourly CO

11   concentration median and interquartile range with whiskers extending from the 5th to the 95th percentile.

12   Data from 2005-2007 were used to generate the box plots which are stratified by season as follows:

13   1 = winter (December-February), 2 = spring (March-May), 3 = summer (June-August), and 4 = fall

14   (September-November). The comparison tables include the Pearson correlation coefficient (r), the 90th

15   percentile of the absolute difference in concentrations (P90) in ppm, the coefficient of divergence (COD)

16   and the straight-line distance between monitor pairs (d) in km. The COD provides an indication of the

17   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

18   where *Xij* and *Xik* represent the observed hourly concentrations for time period *i* at sites *j* and *k*, and *p* is

19   the number of paired hourly observations. A *COD* of 0 indicates there are no differences between

20   concentrations at paired sites (spatial homogeneity), while a *COD* approaching 1 indicates extreme spatial

21   heterogeneity. Similar maps, box plots and comparison tables for the nine remaining CSAs/CBSAs

22   described earlier in this chapter along with Phoenix and Pittsburgh are included in Annex A.

Phoenix Core Based Statistical Area
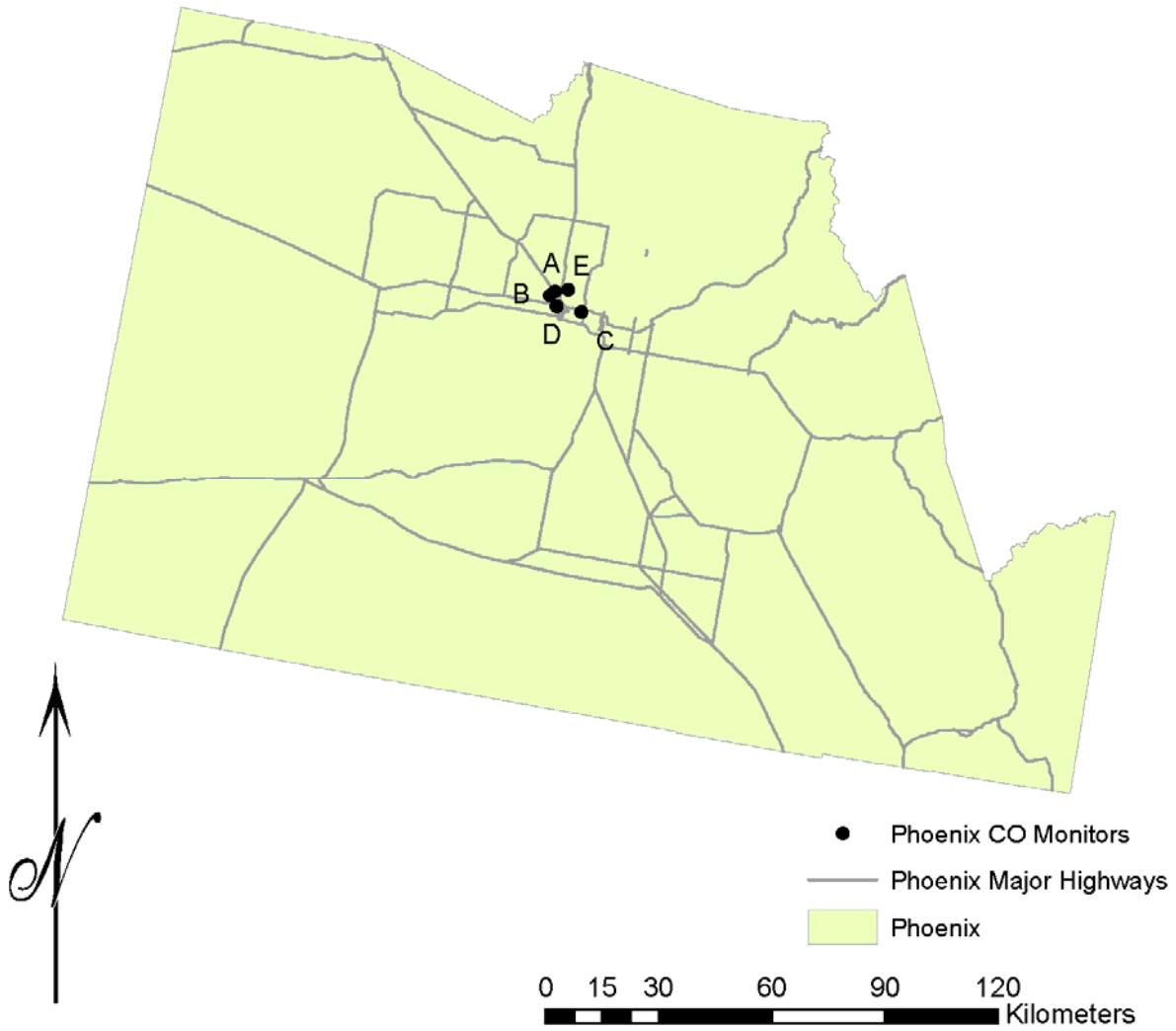
Figure 3-13.   Map of CO monitor locations with AQS Site IDs for Phoenix, AZ.

	A	B	C	D	E
Mean	0.93	0.84	0.58	0.76	0.79
Obs	25382	25589	25657	25414	25435
SD	0.95	0.88	0.64	0.72	0.64
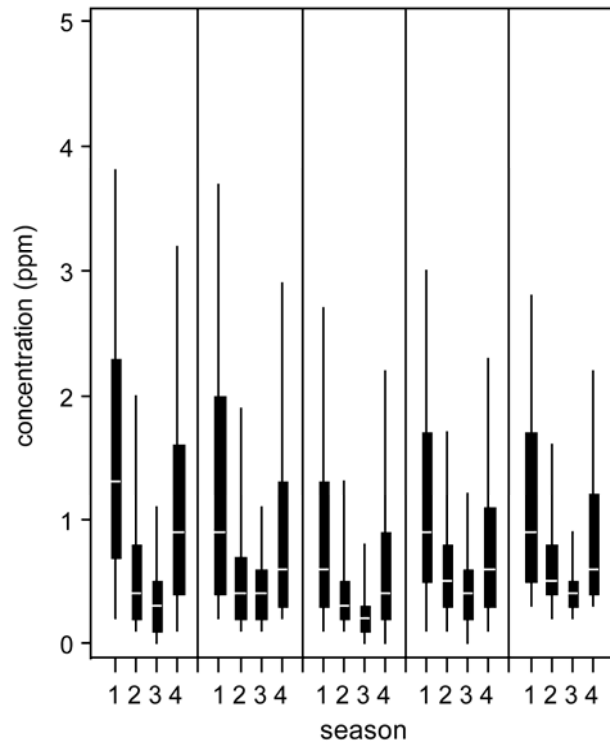
Figure 3-14. **Box plots illustrating the seasonal distribution of 2005-2007 hourly CO concentrations in Phoenix, AZ. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis. The box plots for each monitor include the hourly CO concentration median and interquartile range with whiskers extending from the 5th to the 95th percentile.**

Table 3-7. Table of inter-sampler 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 Phoenix, AZ.

Phoenix

		A	B	C	D	E
A	r	1.00	0.89	0.80	0.86	0.84
	P90	0.0	0.7	1.1	0.8	0.9
	COD	0.0	0.37	0.43	0.39	0.37
	d	0.0	1.6	8.9	3.9	3.5
B	r		1.00	0.81	0.88	0.89
	P90		0.0	0.9	0.6	0.7
	COD		0.0	0.38	0.34	0.24
	d		0.0	9.4	3.4	4.9
C	r			1.00	0.81	0.85
	P90			0.0	0.7	0.6
	COD			0.0	0.41	0.36
	d			0.0	6.6	6.8
D	r				1.00	0.83
	P90				0.0	0.6
	COD				0.0	0.33
	d				0.0	5.2
E	r					1.00
	P90					0.0
	COD					0.0
	d					0.0

Legend
r
P90
COD
d

Pittsburgh Combined Statistical Area

Figure 3-15.   Map of CO monitor locations with AQS Site IDs for Pittsburgh, PA.

	A	B	C	D	E	F	G
Mean	0.28	0.32	0.47	0.28	0.32	0.21	0.07
Obs	25655	25936	25818	25500	25745	25319	25785
SD	0.32	0.26	0.33	0.27	0.26	0.23	0.15
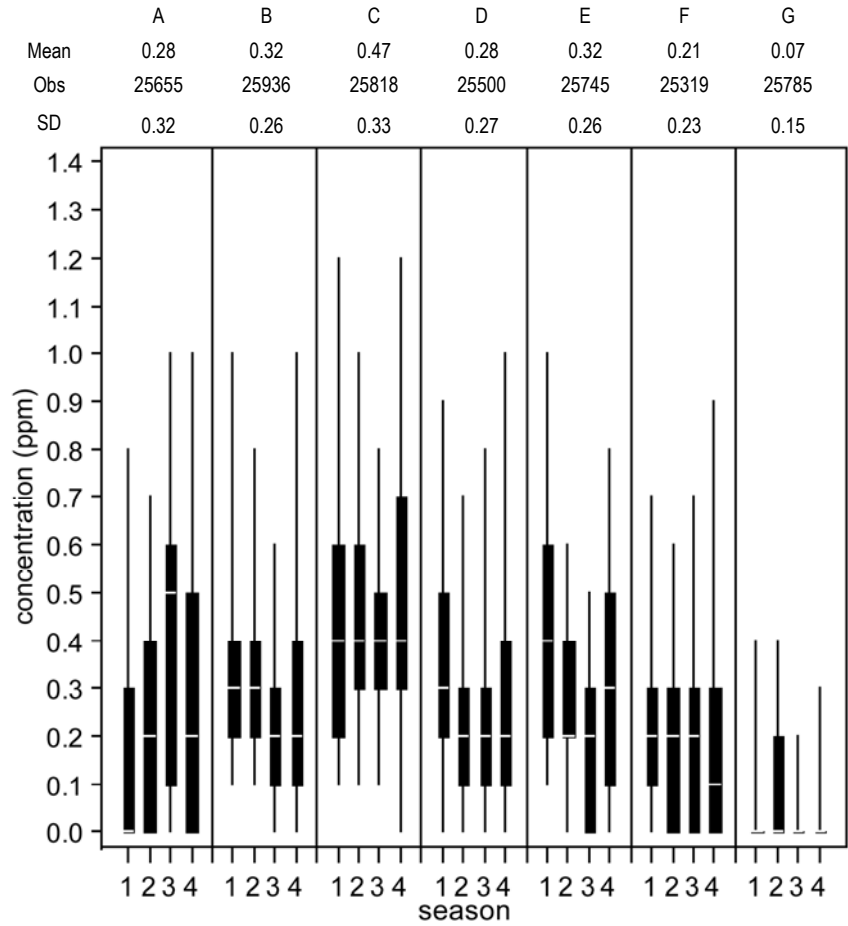
Figure 3-16. **Box plots illustrating the seasonal distribution of 2005-2007 hourly CO concentrations in Pittsburgh, PA. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis. Median interquartile range is shown with whiskers extending from the 5th to the 95th percentile.**

Table 3-8. Table of inter-sampler 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 Pittsburgh, PA.

Pittsburgh	A	B	C	D	E	F	G
A	1.00	0.52	0.43	0.05	0.11	0.42	0.18
	0.0	0.5	0.6	0.7	0.6	0.5	0.7
	0.0	0.69	0.68	0.74	0.72	0.73	0.88
	0.0	2.2	1.8	41.9	66.8	34.4	45.8
B		1.00	0.73	0.30	0.42	0.29	0.35
		0.00	0.40	0.50	0.40	0.50	0.50
		0.00	0.39	0.54	0.51	0.62	0.86
		0.00	0.70	43.40	68.00	33.60	43.70
C			1.00	0.20	0.39	0.25	0.30
			0.0	0.7	0.6	0.7	0.8
			0.0	0.56	0.51	0.65	0.88
			0.0	43.4	68.2	33.3	44.1
D				1.00	0.16	0.09	0.02
				0.0	0.6	0.6	0.7
				0.0	0.57	0.69	0.87
				0.0	27.5	75.0	84.1
E					1.00	0.26	0.21
					0.0	0.5	0.6
					0.0	0.68	0.87
					0.0	101.0	104.1
F						1.00	0.09
						0.0	0.5
						0.0	0.90
						0.0	37.8
G							1.00
							0.0
							0.0
							0.0

Legend
- r
- P90
- COD
- d

1

2   The Phoenix CBSA in Figure 3-13 incorporates an area of 37,786 km^2 with the CO monitors

3 densely packed near the urban center. The maximum straight-line distance between CO monitors in the

4 Phoenix CBSA is 9.4 km. By contrast, the Pittsburgh CSA in Figure 3-15 is less than half the size, having

5 an area of 14,627 km^2, but the monitors are farther apart with a maximum straight-line distance between

6 them of 104.1 km. Of the eleven CSAs/CBSAs investigated, Phoenix has among the highest correlations

7 across monitors, while Pittsburgh has among the lowest. This discrepancy is partly due to the close

8 proximity of the monitors as noted here, but horizontal distance alone does not explain the range of

9 correlations observed between monitors. For example, the three monitors located in the downtown urban

10 core of Pittsburgh (sites A, B and C; AQS site IDs 420030010, 420030031 and 420030038; maximum

1   distance = 2.2 km) exhibited considerably lower correlations (0.43 ≤ r ≤ 0.73) than any of the monitor

2   pairs in Phoenix (0.80 ≤ r ≤ 0.89), located up to 9.4 km apart.

3   The correlation structures for measurements at the monitors in each of the eleven CSAs/CBSAs

4   included in this analysis reveal a wide range of response between monitors in each city and among the

5   cities judged against each other. While this wide range is produced by the interactions of many physical

6   and chemical elements, the location of each monitor and the uniqueness of its immediate surroundings

7   can often explain much of the agreement or lack thereof. Compare, for example, Figures 3-17 and 3-18,

8   the aerial views of monitors C (AQS site ID 040133002) and E (AQS site ID 040139997), respectively, in

9   Phoenix. Monitor C has a correlation value with monitor E of 0.85 even though C is less than 1 km from

10   the intersection of two major highways and E is surrounded by neighborhood residences. Because all

11   other correlations of monitors in Phoenix are also >0.8, the network of CO monitors there appears to have

12   captured the behavior of emitted and transported CO with high fidelity. In contrast, monitors in Pittsburgh

13   show a low degree of correlation, with only two values >0.5 and eight values ≤ 0.2. The topography of

14   Pittsburgh is mountainous and therefore more complex than that of Phoenix, and this could account for

15   some of the disparity across space. But in addition, several CO monitors in Pittsburgh are sited at

16   distances far from the urban core, making them less likely to correlate with those monitors in the high-

17   density urban core. Figure 3-19 depicts the three monitors in the Pittsburgh urban core (monitor A: AQS

18   site ID 420030010, monitor B: AQS site ID 420030031, and monitor C: AQS site ID 420030038), which

19   demonstrated the highest correlation values in this CSA for 2005-2007. Figure 3-20 shows the location of

20   a more distant monitor, monitor F (AQS site ID 421250005), which does not correlate well with the three

21   monitors located downtown, very likely because it is located at a great distance from any strong CO

22   sources in the downtown urban core. This analysis demonstrates that agreement between monitors on an

23   urban scale is a complex function of monitor siting, location to sources, geography, and

24   micrometeorology.

25   In addition to high correlations, Phoenix exhibits similar average concentration levels across

26   monitors with 0.24 ≤ COD ≤ 0.43; see Table 3-7. The seasonal patterns shown in Figure 3-14 also

27   demonstrate homogeneity across monitors for Phoenix. By contrast, Pittsburgh had more variability

28   between monitored values at the sites shown in Figure 3-16 with the range in COD shifted upward

29   (0.39 ≤ COD ≤ 0.90); see Table 3-8. For the three sites located in the downtown urban core of Pittsburgh

30   (sites A, B and C), the COD is as high as 0.69, indicating greater spatial variability in CO concentrations

31   in Pittsburgh, even for these more proximal monitors.

32   The information in Table 3-8 should be used with some caution since many of the reported

33   concentrations for the years 2005-2007 are very near or even well below the monitors' stated lowest

34   detection limits. Because ambient concentrations are now in large part very near to the FRM detection

35   limit of 1.0 ppm and the coarsely reported measurement resolution is 0.1 ppm, the comparison statistics

36   shown in these tables might be biased to show a specious heterogeneity in the box plots. These cautions

1   are especially important for interpreting data from site G in Pittsburgh and selected other sites in other

2   metropolitan regions where one or more monitors consistently reported values below the stated detection

3   limit. Such monitors include Houston site D, AQS site ID 482011035, and New York site I, AQS site ID

4   361030009, included in Annex A.
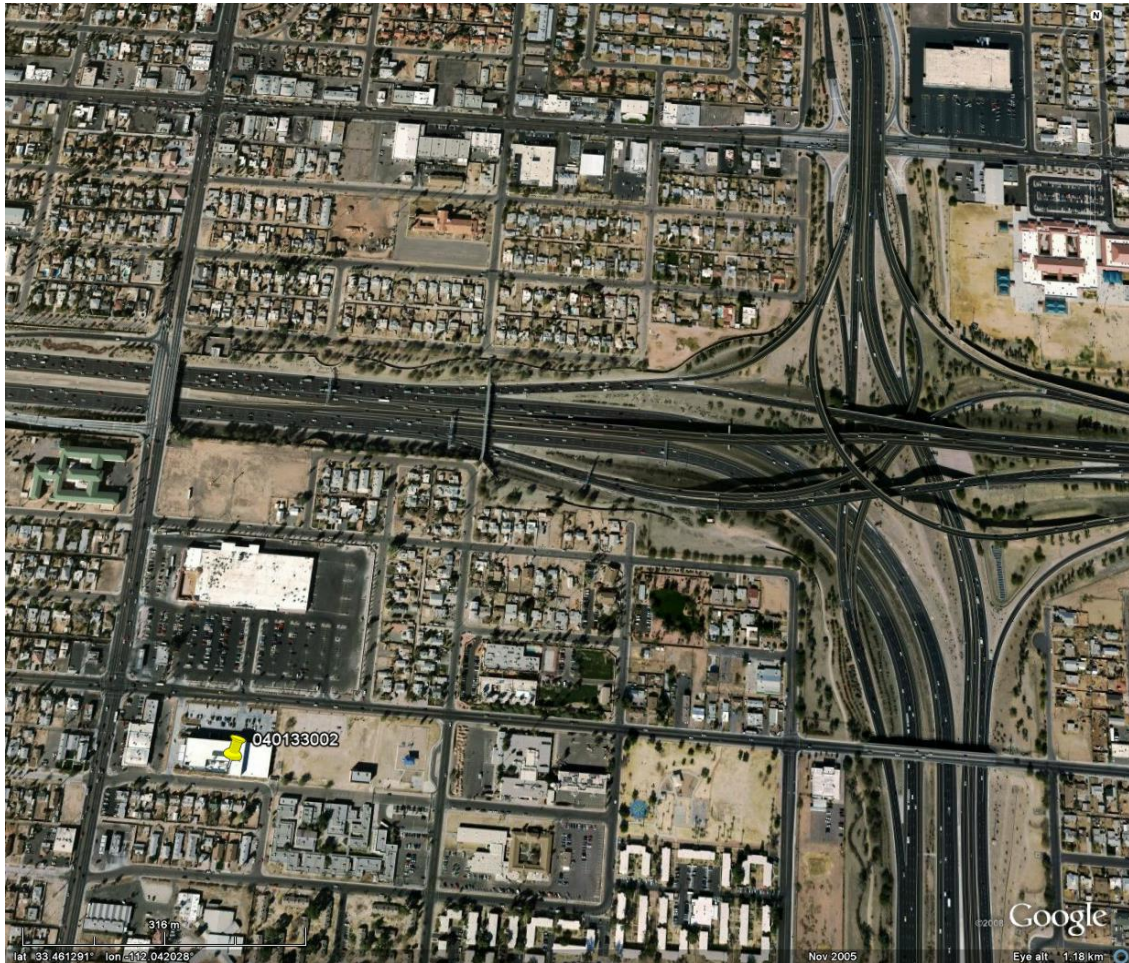
Figure 3-17.   **Aerial view of the location of CO monitor C. AQS ID 040133002 (marked by the yellow pin) in Phoenix, AZ, depicting its proximity to major roadways and neighborhood residences.**
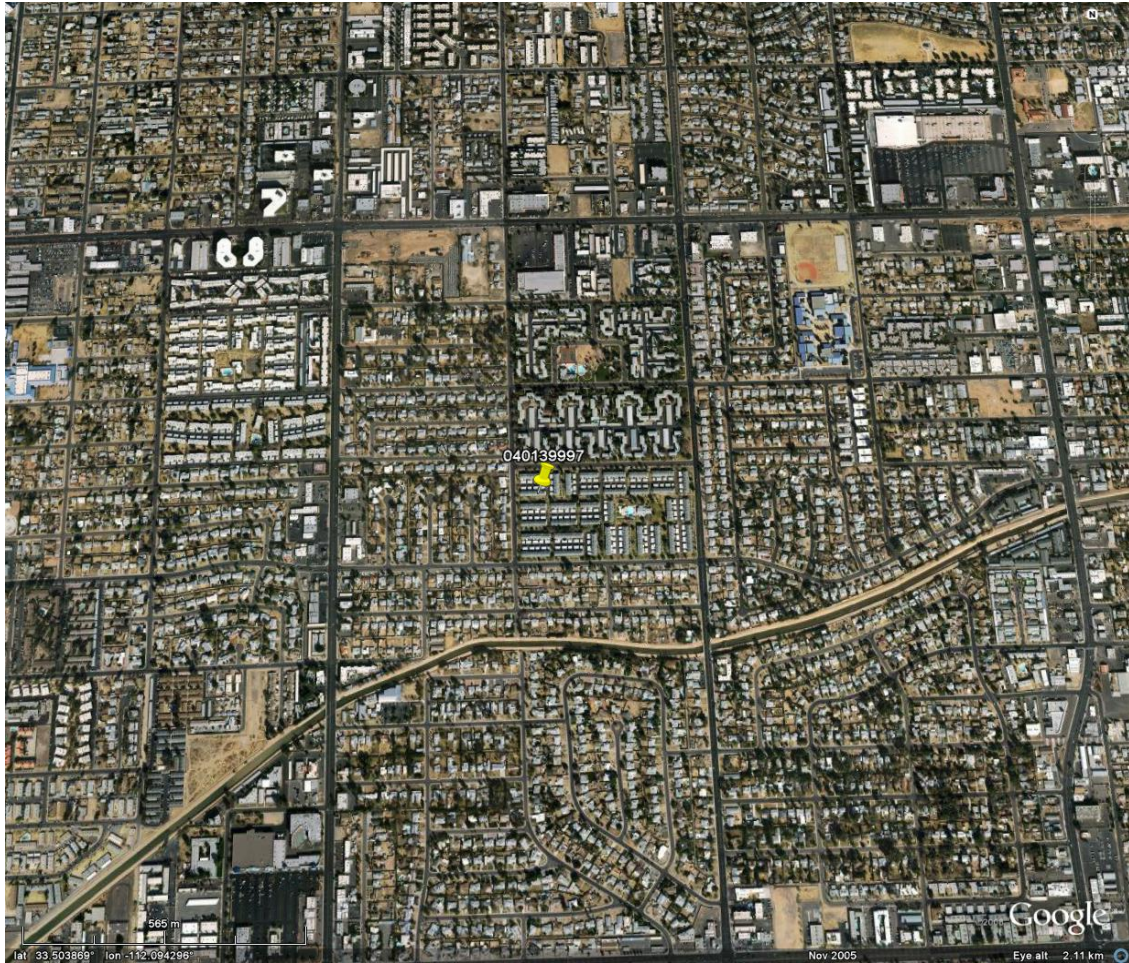
Figure 3-18. Aerial view of the location of CO monitor E. AQS ID 040139997 (marked by the yellow pin) in Phoenix, AZ, depicting its proximity to neighborhood residences and secondary surface roads.

Figure 3-19. Aerial view of the location of CO monitors A, B, and C. AQS IDs 420030010, 420030031, and 420030038 (marked by yellow pins) in Pittsburgh, PA, depicting their proximity to major roadways and areas of high commercial density.

Figure 3-20. **Aerial view of the location of CO monitor F. AQS ID 421250005 (marked by the yellow pin) in the Pittsburgh, PA CSA, depicting its proximity to secondary surface roads and water ways.**

3.5.1.3. Neighborhood Scale

1   Roadway density is an important determinant of the spatial distribution of CO concentrations in
2   urban areas. Mobile sources are the largest single source of CO, and their abundance and density affect
3   the magnitude of CO production. Urban topography around roadways also affects CO transport and
4   dispersion (e.g., Mfula et al., 2005; Rigby and Toumi, 2008). CO concentration gradients have been
5   observed in near-road environments (Baldauf et al., 2008; Pirjola et al., 2006; Zhu et al., 2002) such that
6   CO concentrations are often higher on or near roadways compared with upwind sites, and can decrease
7   with increasing distance from the road. For example, Zhu et al. (2002) found that on-road CO
8   concentrations were approximately 10 times higher than at an upwind monitoring site, as shown in Figure
9   3-21. At 30 m downwind from the road, relative CO concentrations were decreased to 7 times above
10   upwind levels, and were approximately 2.5 times the upwind levels at 100 m. Concentrations continued to

1   decrease and were still somewhat higher than upwind levels at the final monitoring site 300 m away.

2   Other traffic-related pollutants (BC, particle number) followed a similar pattern, although with different

3   downwind:upwind ratios. This indicates that near-road and on-road exposures are important in CO

4   exposure assessment.

5   Field measurements, computational modeling, and wind tunnel experiments have shown that

6   roadway design and roadside features can affect CO and other pollutant concentrations near roadways.

7   Field measurements reported by Baldauf et al. (2008) indicated that noise barriers could reduce near-road

8   pollutant concentrations by as much as 50 percent, although this effect was highly dependent on

9   meteorological conditons. This study also showed that the presence of mature vegetation, where the noise

10   barrier further reduced concentrations and flattened the concentration gradient away from the road. Urban

11   dispersion and wind-field modeling by Bowker et al. (2007) also demonstrated the influence of noise

12   barriers and vegetation on the concentrations and spatial variability of inert pollutants emitted from traffic

13   sources. Wind tunnel work reported by Baldauf et al. (In press) demonstrated the effects of noise barriers

14   as well as roadway design characteristics, such as the presence of cut and elevated roadway segments.

15   These results indicated that cut sections reduced concentrations and altered the gradient away from the

16   road for inert gases emitted from traffic sources such as CO. These results showed similar concentrations

17   as Zhu et al. (2002) for roadway segments at-grade with no obstructions to air flow as well as elevated

18   roadway segments with fill conditions.

19   The geometry of urban street canyons has a profound effect on the distribution of CO

20   concentrations on a micro-scale. A number of studies have performed computational and wind tunnel

21   modeling of street canyons using nonreactive tracers and demonstrated the potential variability in

22   concentration within a canyon (e.g., Borrego et al., 2006; Chang and Meroney, 2003; Kastner-Klein and

23   Plate, 1999; So et al., 2005; Xiaomin et al., 2006). Because CO is a pollutant with very low reactivity on

24   urban and regional scales, results from these models are directly relevant to CO concentration

25   distributions in street canyons. Influential parameters include canyon height to width ratio (H/W), source

26   positioning, wind speed and direction, building shape, and upstream configuration of buildings.

27   Figure 3-22 shows dimensionless concentrations obtained from wind tunnel and computational fluid

28   dynamics simulations of tracer gas transport and dispersion in an infinitely long street canyon with a line

29   source centered at the bottom of the canyon (Xiaomin et al., 2006). When the canyon height was equal to

30   the street width (typical of moderate density suburban or urban fringe residential neighborhoods) and

31   lower background wind speed existed, concentrations on the leeward (downwind) canyon wall were four

32   times those of the windward (upwind) wall near ground level. When the canyon height was twice the

33   street width (typical of higher-density cities) and background winds were somewhat higher, near ground-

34   level concentrations on the windward canyon wall were roughly three times higher than those measured at

35   the leeward wall. These results suggest that the magnitude of microscale CO concentrations may vary by

36   factors of three or four times at different locations within a street canyon.
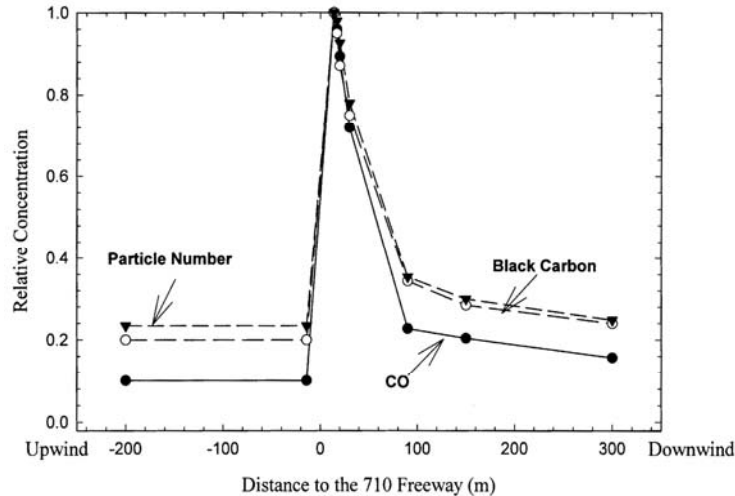
Source: Zhu et al. (2002)

Figure 3-21.   Relative concentrations of CO and copollutants at various distances from the 710 freeway in Los Angeles.

1   In a multi-site survey of curbside CO concentration in London, U.K., Croxford and Penn (1998)
2   observed differences in concentration related to the side of the street on which the monitor was positioned
3   relative to the wind direction. Bogo et al. (2001) measured CO concentrations in a street canyon with
4   building height-street width ratio of 1 in Buenos Aires, Argentina using a continuous CO monitor. Similar
5   to the Xiaomin et al. (2006) simulation results for a height-width ratio of 1, Bogo et al. (2001) observed
6   slightly higher leeward concentrations than windward concentrations within the canyon, where
7   recirculating airflow inside the canyon causes pollutants to collect in higher concentration on one side.
8   For part of this study, they estimated aggregated emissions from several fixed sources, including thermal
9   power stations and home heating, and from traffic. Mobile source emissions were estimated to be more
10   than 800 times higher than fixed source emissions given assumptions regarding vehicle fleet. Moreover,
11   they estimated that up to 30% of the measured CO concentrations came from within the local street
12   canyon in which measurements were made.
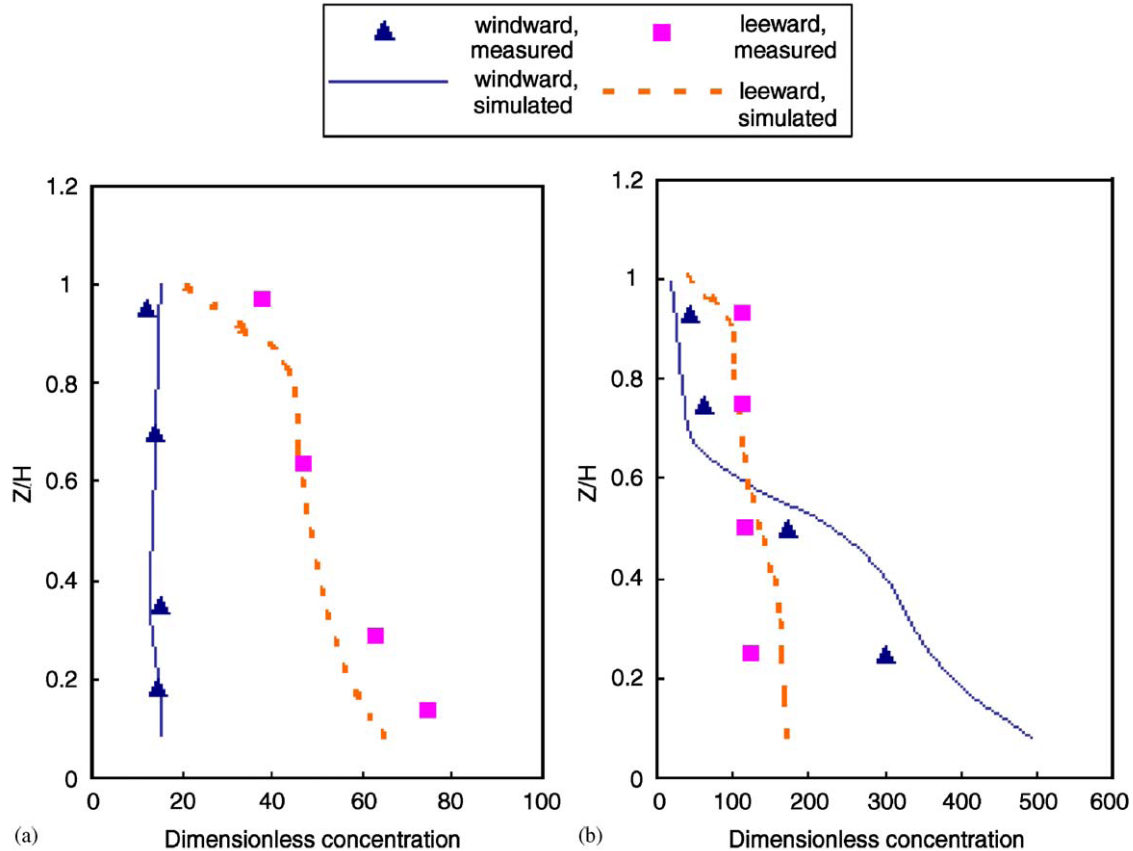
Figure 3-22. **Dimensionless tracer gas concentration as a function of elevation at windward and leeward locations and street canyon aspect ratios (H/W). Z/H is the elevation of the measurement (Z) scaled by building height (H). (a) Dimensionless concentration on the windward and leeward sides of the canyon when H/W = 1 and wind speed = 3 m/s. (b) Dimensionless concentration on the windward and leeward sides of the canyon when H/W = 2 and wind speed = 5 m/s. Computational fluid dynamics modeling was performed, and measurements were obtained in wind tunnel simulations.**

1   Identification of neighborhood-scale variability is important for interpreting data from ambient CO

2   monitors. Figure 3-23 shows a scatter plot of CO correlation as a function of distance (Pearson r) for

3   monitors sited within 4 km of each other in four of the eleven CSAs and CBSAs. (The other seven CSAs

4   or CBSAs were excluded from this analysis because their monitors were spaced farther than 4 km from

5   each other.) The purpose of this plot is not to show a simple relationship between inter-sampler

6   correlation and distance but to illustrate how this relationship varies between cities at the neighborhood

7   scale. High correlation is seen for the monitors in the Phoenix, AZ CBSA, while those in the Pittsburgh,

8   PA, CSA have much lower inter-sampler correlations with steeper slope ($\Delta r/\Delta d$ = -0.04 for Phoenix and

9    $\Delta r/\Delta d$ = -0.27 for Pittsburgh). The inter-sampler correlation observed for the Boston, MA CSA is also

1   substantially lower than those observed for Phoenix. As discussed in section 3.5.1.2, these differences

2   could be due to a variety of factors, including but not limited to natural and urban topography, different

3   traffic conditions on roads located near monitors, and proximity of the monitors to the roadway.
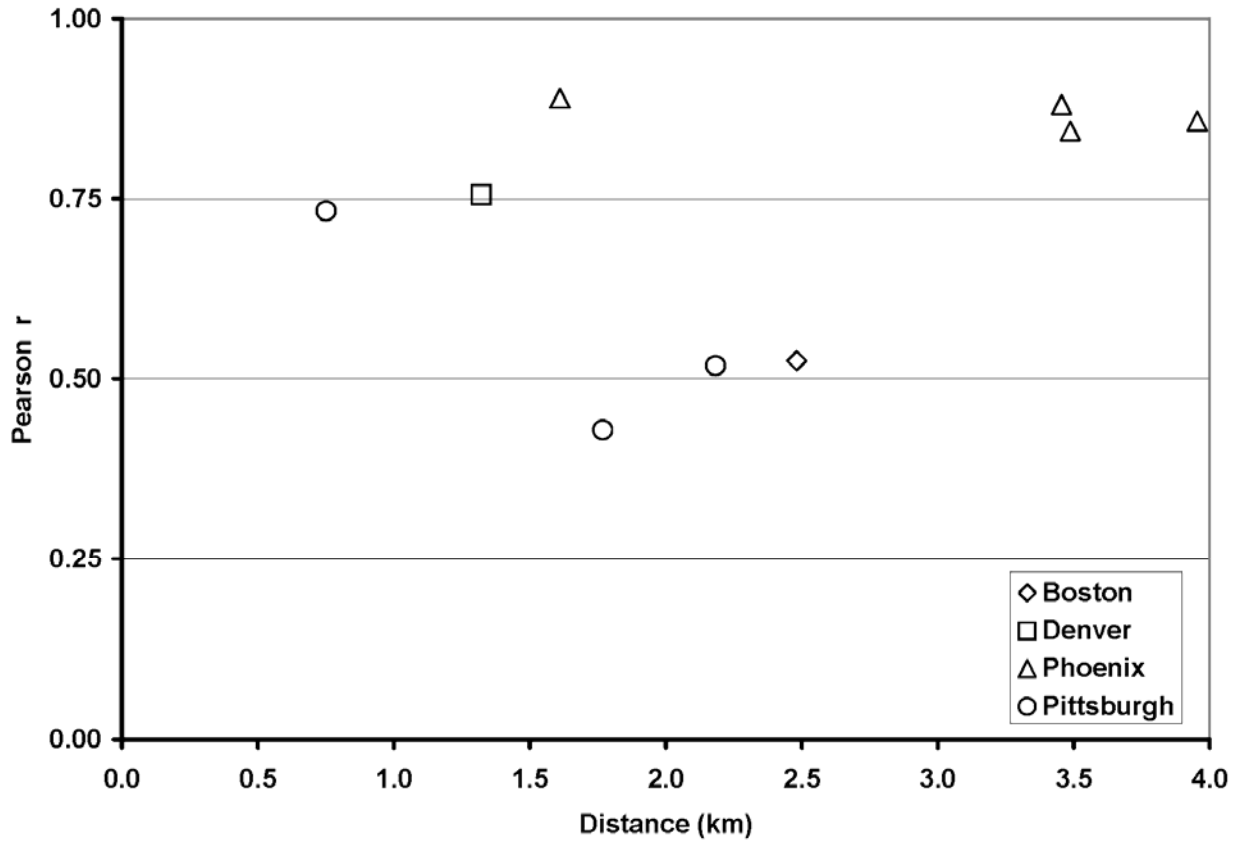
Figure 3-23.   **Inter-sampler correlations as a function of distance between CO monitors for samplers located within 4 km (neighborhood scale) for Boston, Denver, Phoenix, and Pittsburgh.**

3.5.2. Temporal Variability

3.5.2.1. Multi-year Trends

1   Figures 3-24 (top) shows ambient CO concentrations in ppm from 1980 to 2006 based on
2   continuous measurements averaged over 8-h time segments. The 8-h NAAQS is indicative of exposures
3   occurring over a sustained period of time, an outdoor worker's exposure over the course of a day, for
4   example. Figure 3-24 (bottom) depicts trends in the annual second-highest 8-h CO concentrations for 144
5   sites in 102 counties nationwide having data either in the State and Local Air Monitoring Stations
6   (SLAMS) network or from other special purpose monitors.
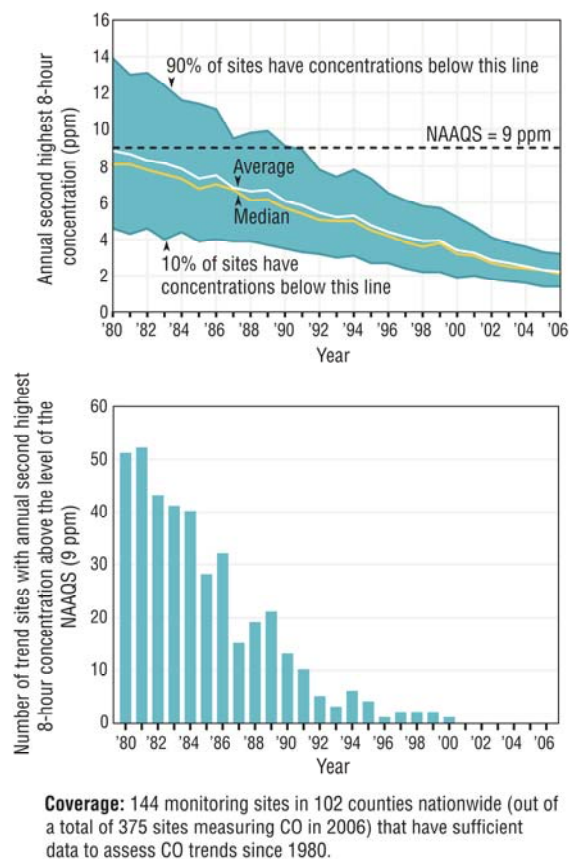
Source: U.S. EPA (2008c)

Figure 3-24. **(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).**

1   The 2006 annual second highest 8-h CO concentration averaged across 144 monitoring sites

2   nationwide was 75% below that for 1980, and is the lowest concentration recorded during the past 27

3   years; see Figure 3-24 (top). Since 1992, more than 90% of all these sites have reported CO

4   concentrations below the 8-h NAAQS of 9 ppm; see Figure 3-24. The mean annual second highest 8-h

5   ambient CO concentration has been below 5 ppm since 2004. The downward trend in CO concentrations

6   in the 1990s parallels the downward trend observed in CO emissions, attributed largely to decreased

7   mobile source emissions; see Figure 3-2. In addition, of the 144 sites used to determine this trend, from a

8   total of 375 monitoring sites operating in 2006, the number reporting second-highest CO concentrations

9   above the level of the CO NAAQS declined to zero over the same period; see Figure 3-24 (bottom).

10   Consistent with the nationwide trends in emissions and concentrations, CO concentrations in all ten

11   EPA Regions have steadily decreased since 1980, with reductions over this period ranging from 68% in

12   Region 7 to 85% in Region 1; see Figure 3-25. This is also consistent with declining emissions seen in

13   many regions of the U.S., shown in Figure 3-4. Reductions in anthropogenic CO emissions in the U.S.

14   and elsewhere in the extra-tropical northern hemisphere are a major cause for the observed decrease in

15   hemispheric and global-average CO concentrations observed since 1991 (Bakwin et al., 1994), although

16   ~30% of the decline between 1991 and 2001 was attributed to decreases in CO following the eruption of

17   Mt. Pinatubo (Novelli et al., 2003).
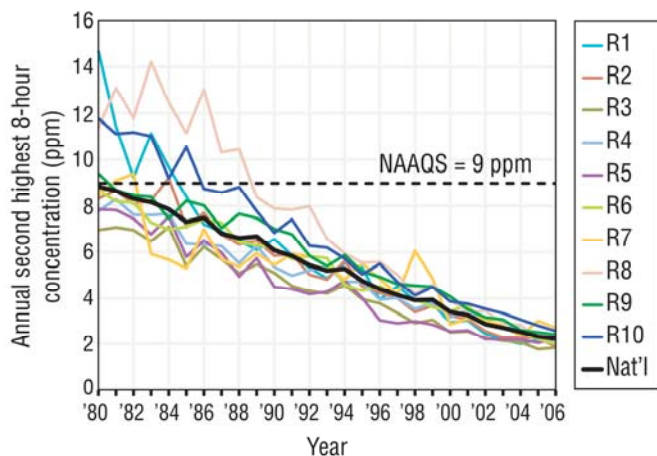
Coverage: 141 monitoring sites in the EPA Regions (out of a total of 375 sites measuring CO in 2006) that have sufficient data to assess CO trends since 1980.

Source: U.S. EPA (2008c)

Figure 3-25. **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

1   Weekday and weekend diel variation for the mean, median, 5th, 10th, 90th, and 95th percentiles of

2   hourly CO concentration over 2005-2007 are shown in Figures 3-26 and 3-27, respectively among the

3   eleven CSAs and CBSAs examined in this assessment. The weekday data showed that the Anchorage

4   mean, median, 5th and 10th percentile CO concentration curves exhibit more pronounced morning and

5   evening rush hour peak CO levels. Boston, Denver, Houston, Los Angeles, Phoenix, Pittsburgh, and St.

6   Louis all exhibited similar trends, although the magnitude of the concentrations shown was roughly twice

7   as high for Anchorage as the other cities. The curves had less overall variability for Boston, Pittsburgh,

8   and St. Louis. The Atlanta plot shows that the median concentration was fairly constant throughout the

9   24-h period, with a slightly elevated mean during the morning hours. The 90th and 95th percentile curves

10   exhibit stronger morning and evening CO concentration peaks. New York City shows fairly constant CO

11   mean and median concentration throughout the day with slight elevations throughout the morning rush

12   hour and a slight trough between 1:00 and 5:00 AM. The Seattle plot shows a daytime plateau beginning

13   around 5:00 AM and lasting until roughly 10:00 PM, with higher concentrations during morning and

14   afternoon rush hour. Differences in hourly variation among the eleven CSAs and CBSAs reflect city-to-

1   city variation in source characteristics and meteorology. For instance, the rush hour peaks in many cities

2   likely correspond to increased mobile source emissions during those periods. Local meteorology and

3   topography, which influence mixing heights, can also affect hourly variation in CO concentration.

4   Figure 3-27 illustrates weekend diel trends for the eleven CSAs and CBSAs considered in this

5   assessment. For Anchorage during the period 2005-2007, the mean and median concentration curves

6   peaked during the morning and evening hours. A daytime concentration trough is evident. The 90th and

7   95th percentiles of concentration were similar but more pronounced. The shape of this plot is also

8   characteristic of Atlanta, Boston, Denver, Houston, Los Angeles, Phoenix, Pittsburgh, Seattle, and St.

9   Louis, although the Anchorage CO concentrations are nearly 100% higher than concentrations in the other

10   cities. The weekend diel plot for New York shows that the mean and median CO concentrations remain

11   fairly constant throughout the day, with a slight reduction between 2:00 and 7:00 AM. The 90th and 95th

12   percentile curves illustrate more diel variation.
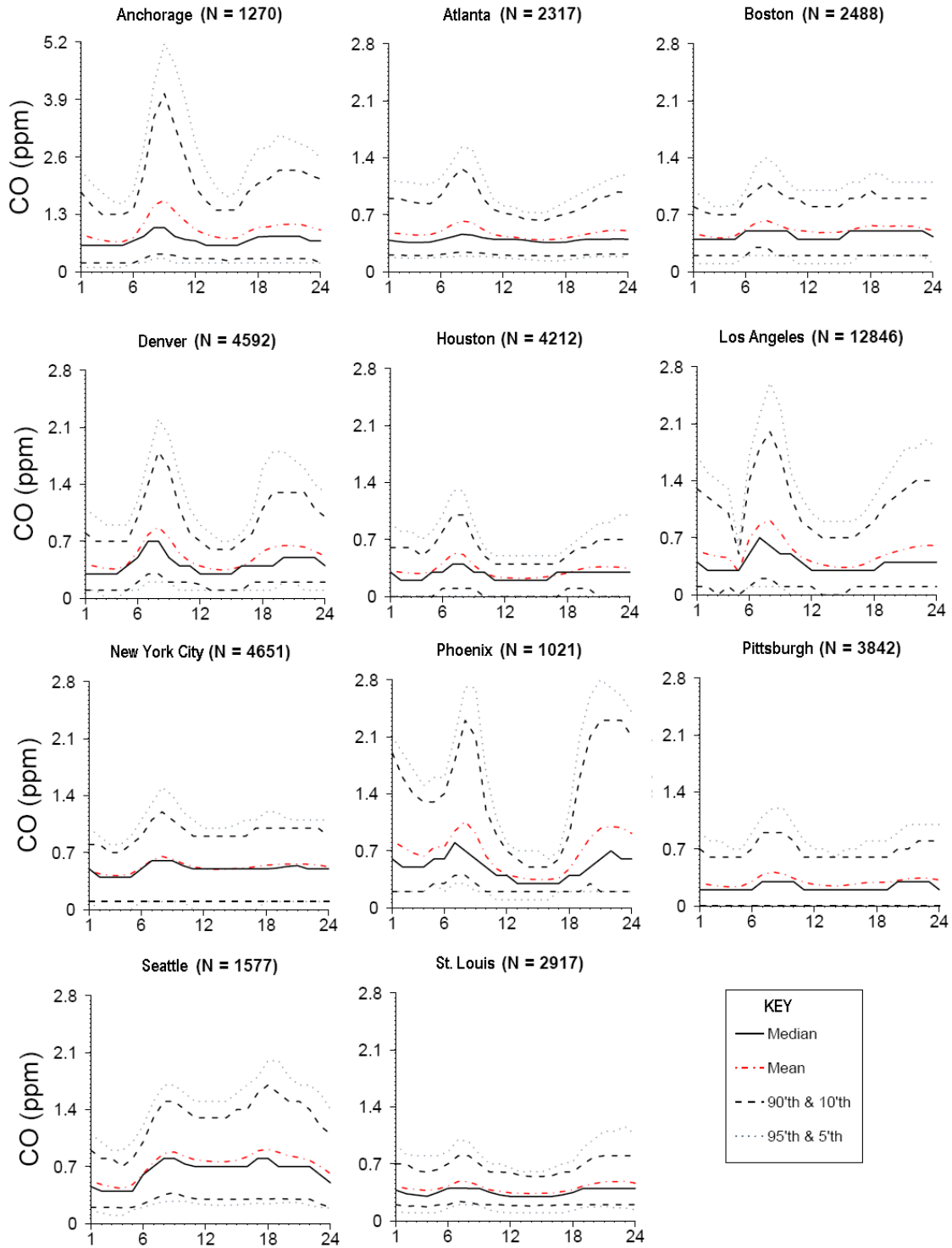
Figure 3-26. Diel plot generated from weekday hourly CO data (ppm) for the eleven CSAs and CBSAs 2005-2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles of CO concentration. Note that the y-axis of the Anchorage CBSA plot is scaled to 5.2 ppm while the other plots are scaled to 2.8 ppm.
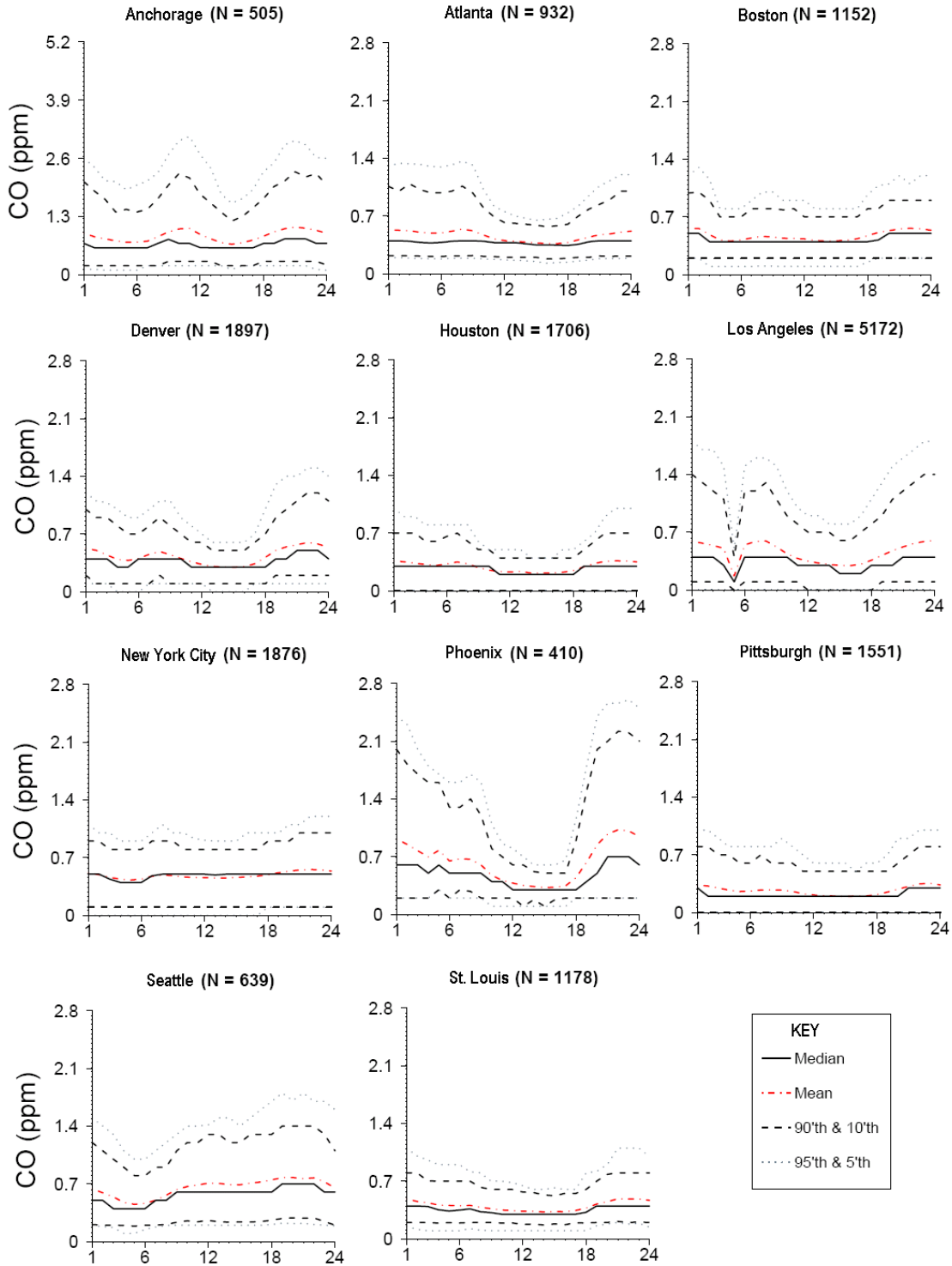
Figure 3-27. Diel plot generated from weekend hourly CO data (ppm) for the eleven CSAs and CBSAs 2005-2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles of CO concentration. Note that the y-axis of the Anchorage CBSA plot is scaled to 5.2 ppm while the other plots are scaled to 2.8 ppm.

3.5.3. Associations with Copollutants

1   Associations between hourly CO and other copollutants, including SO_2, NO_2, O_3, PM_{10}, and $PM_{2.5}$

2   are provided in box plots for all U.S. monitors in Figure 3-28. The figure also shows the correlation of the

3   24-h avg CO concentration with the daily max 1-h and daily max 8-h CO concentrations as well as the

4   correlation between the daily max 1-h and daily max 8-h concentrations. AQS data were obtained from all

5   available co-located monitors across the U.S. after application of 75% completeness criteria. Pearson

6   correlation coefficients (r) were calculated using 2005-2007 data. Correlation plots analogous to Figure 3-

7   28 for select individual cities are provided in Annex A.
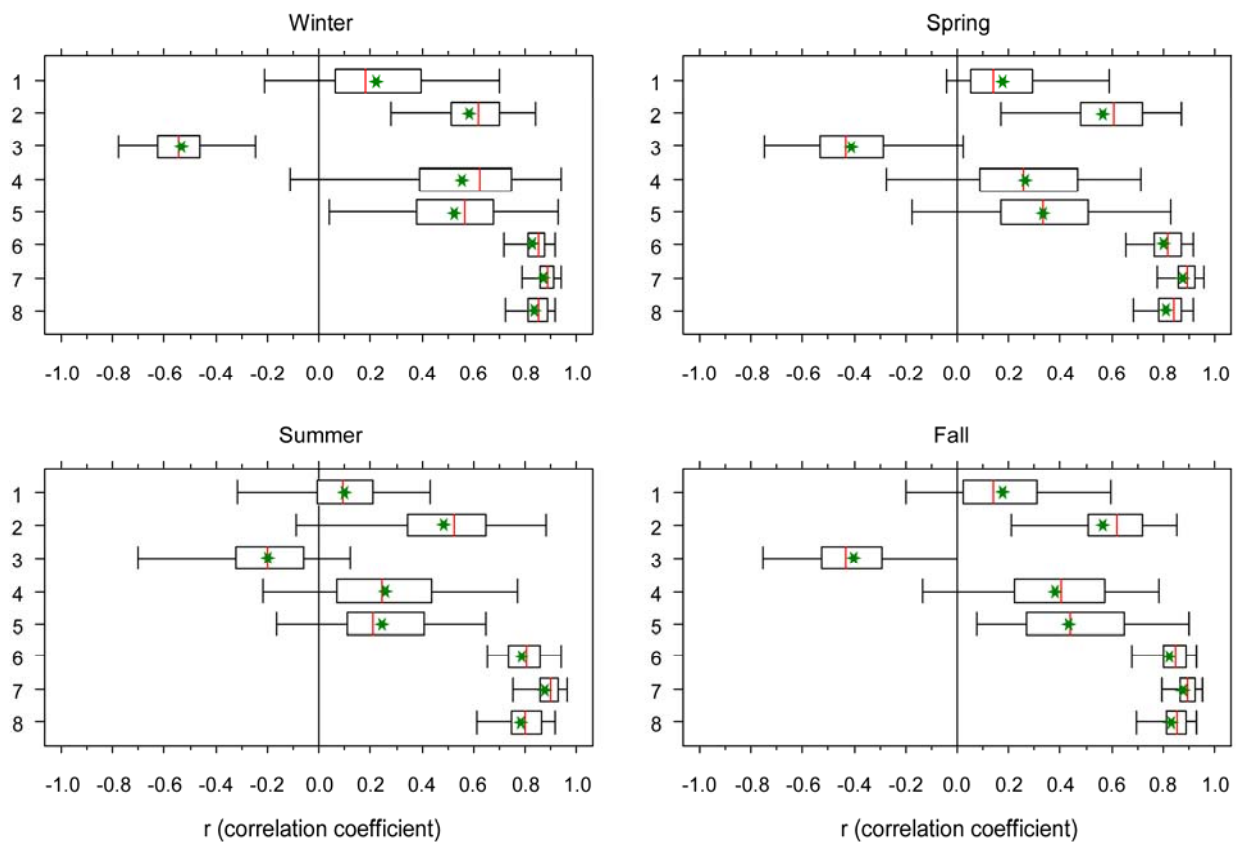
Figure 3-28.   **Seasonal plots of nationwide correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. (The numbers in this caption refer to those on the y-axis of each seasonal plot.) Red bars denote the median, and green stars denote the arithmetic mean.**

1   The nationwide mean and median of the correlation with CO were positive for NO_2, PM_{10}, and

2    $PM_{2.5}$; near zero for SO_2^-; and negative for O_3. These findings might reflect common combustion sources

3   for CO, NO_2, and $PM_{2.5}$. In all cases, a wide range of correlation values were reported. There were

4   significant positive correlations for all CO-CO (24-h avg, daily max 1-h, daily max 8-h) comparisons

5   rendered. Among those copollutants with positive associations, NO_2 had the highest mean and median

6   correlations, followed by $PM_{2.5}$ and PM_{10} (correlations vary by season). The correlations of CO with SO_2

7   and PM_{10} were not significantly different from zero for any season; SO_2 would not be expected to

8   correlate well with CO because SO_2 emanates primarily from industrial sources. Correlations between CO

9   and NO_2 were significant and positive for winter, spring, and fall. Correlations between CO and $PM_{2.5}$

10   were significant and positively correlated for winter and fall. Correlations between CO and O_3 were

11   significant and negative for winter only, when CO emissions tend to be high and O_3 formation is low. The

12   copollutant correlation plots for individual cities shown in Annex A illustrate higher and more statistically

13   significant correlations of CO with both PM_{10} and $PM_{2.5}$ in several but not all of the select cities

14   displayed. It is widely believed that sources of CO and $PM_{2.5}$ are highly correlated because they are both

15   emitted directly during incomplete combustion and because secondary nitrate PM comes from NO_X,

16   which is largely produced from mobile sources. The wide confidence intervals displayed in the

17   nationwide plots reflect the large pool of data in addition to the micrometeorological factors in each city.

18   Additionally, CO monitors tend to be located apart from other pollutant monitors based on the criteria

19   from the CFR of siting at least one monitor near the highest source of CO. Lack of co-location can affect

20   the correlation of reported CO with PM_{10} and $PM_{2.5}$ concentrations; this limitation also would inhibit the

21   significance of correlations between CO and $PM_{10-2.5}$.

22   Several studies reported correlations between ambient CO and copollutants. Reported relationships

23   were generally consistent with the correlation data reported by the AQS. Sarnat et al. (2001) reported

24   significant positive Spearman's correlations of CO with NO_2 (r = 0.76) and $PM_{2.5}$ (r = 0.69) and

25   significant negative correlations of CO with O_3 (r = -0.67) in Baltimore. Correlation of CO with SO_2 was

26   insignificant (r = -0.12). The Sarnat et al. (2001) study focused on correlations of ambient and personal

27    $PM_{2.5}$ with gaseous copollutants, so seasonal information is only available for the correlation between

28    $PM_{2.5}$ and CO. High correlation of ambient CO with NO_2 is expected given that both are closely related to

29   mobile source combustion emissions. Sarnat et al (2005) also reported significant year-round association

30   between CO and $PM_{2.5}$ and significant associations between CO and SO_4^{2-} aerosols. Tolbert et al. (2007)

31   reported correlations between multiple pollutants in Atlanta and also showed the highest Spearman's

32   correlation for CO with NO_2 (r = 0.70). CO was also reported to have fairly high correlation with $PM_{2.5}$

33   elemental carbon (EC) (r = 0.66), $PM_{2.5}$ organic carbon (OC) (r = 0.59), and $PM_{2.5}$ total carbon (TC)

34   (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-}

35   (r = 0.14). Kim et al. (2006) measured CO, NO_2, and $PM_{2.5}$ at ambient fixed sites in Toronto, Canada and

1   found associations, averaged over monitoring stations, of CO with $PM_{2.5}$ (Spearman's r = 0.38, non-
2   significant) and of CO with NO_2 (r = 0.72, significant).

3.5.4. Policy-Relevant Background

3   Background concentrations of pollutants used for informing policy decisions about national
4   standards in the U.S. are commonly referred to as policy-relevant background (PRB) concentrations. PRB
5   concentrations are those that are exclusive of anthropogenic emissions in the U.S., Canada and Mexico
6   (North America), and consist of world-wide biogenic emissions (including North America) and
7   anthropogenic emissions elsewhere in the world.
8   PRB concentrations of CO can best be determined from the extensive and long-running network
9   of remote-site baseline CO measurements conducted by NOAA's Earth System Research Laboratory
10 (ESRL), Global Monitoring Division (GMD), as part of their Carbon Cycle Greenhouse Gases Group
11 (CCGG) Cooperative Air Sampling Network (CASN) (http://www.esrl.noaa.gov/gmd/ccgg/iadv). CO data
12 through December 2007 are available with extensive quality assurance and control information from a
13 worldwide network of 72 nodes active in December 2008. ESRL GMD uses the highly sensitive gas
14 chromatography-mercury liberation photometric detection technique with precision to 1 parts per billion
15 (ppb) in 50 ppb (2 ppb in 200 ppb) and accuracy to 1.5 ppb in 500 ppb (2 ppb in 200 ppb) (Novelli et al.,
16 2008).
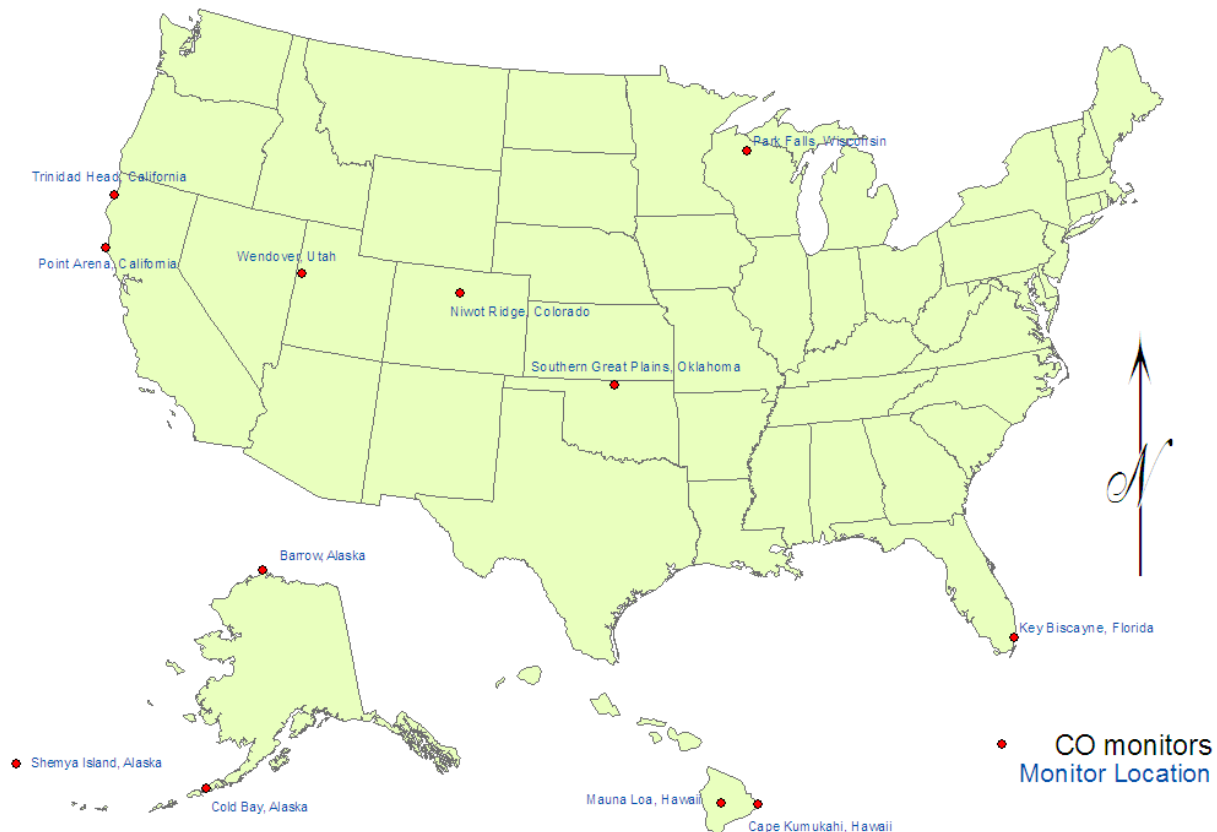
Figure 3-29. Map of the baseline monitor sites used in this assessment to compute policy-relevant background concentrations.

1   This assessment used data from 2005 through 2007 at 12 remote sites in the U.S. to determine PRB
2   (see the map in Figure 3-29): Cold Bay, AK; Barrow, AK; Shemya Island, AK; Cape Kumukahi, HI;
3   Mauna Loa, HI; Trinidad Head, CA; Point Arena, CA; Wendover, UT; Niwot Ridge, CO; Park Falls, WI;
4   Southern Great Plains, OK; and Key Biscayne, FL. Average concentrations for each month and for each
5   year, 2005-2007 are shown for each site in Figure 3- 30. All sites demonstrate the well-known seasonality
6   in background CO with minima in the summer and fall and maxima in the winter and spring. Summer-
7   time minima may be related to photochemical reaction of CO with OH, as described in section 3.3.
8   Analysis for North American PRB is made here by segregating the three Alaska sites (based on their high
9   latitude) and the two Hawaii sites (based on their distance from the continent) and treating the remaining
10   seven sites as representative of the CONUS background. The 3-year avg CO PRB in Alaska ranged from
11   127 to 135 ppb with an average of 130 ppb; in Hawaii from 95.3 to 103.1 ppb with an average of 99.2
12   ppb; and over the CONUS from 118 to 146 ppb with an average of 132 ppb.
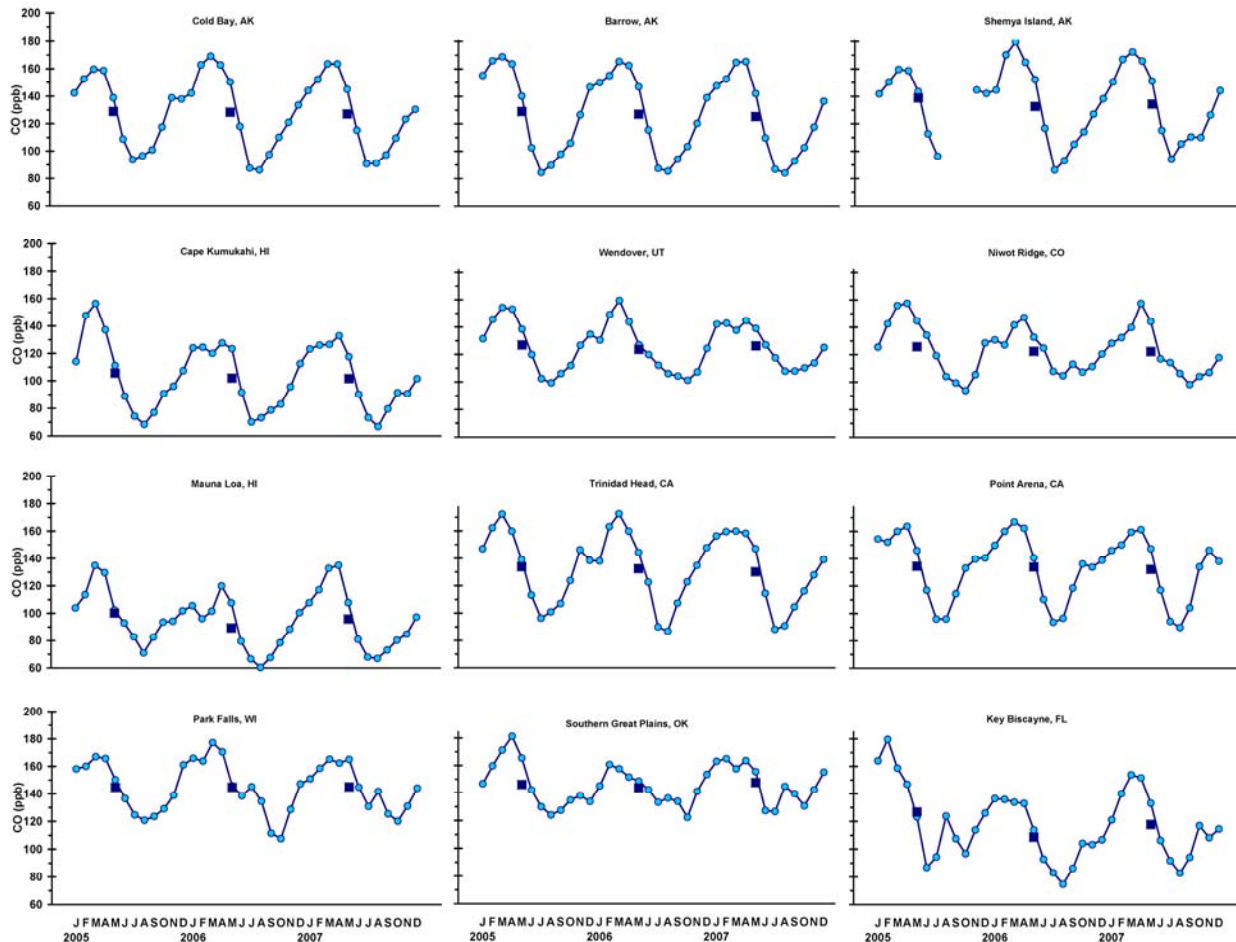
Figures 3-30.   **Monthly (circles) and annual (squares) average CO concentrations (ppb), 2005-2007 . Cold Bay, AK; Barrow, AK; Shemya Island, AK; Cape Kumukahi, HI; Wendover, UT; Niwot Ridge, CO; Mauna Loa, HI; Trinidad Head, CA; Point Arena, CA; Park Falls, WI; Southern Great Plains, OK; and Key Biscayne, FL.**

3.6. Issues in Exposure Assessment

3.6.1. Summary of Findings from 2000 CO AQCD

1   The 2000 CO AQCD (U.S. EPA, 2000) describes the results of studies completed prior to 1999 on

2   personal exposures and microenvironmental concentrations of CO. Although these studies may no longer

3   be representative of current exposure levels due to declining ambient CO concentrations, the personal-

4   microenvironmental-ambient relationships are still instructive. Time spent commuting, particularly in

5   cars, was a major contributor to personal CO exposures. Many studies measured in-vehicle concentrations

6   of CO and found elevated concentrations compared to fixed-site monitors. Roadside CO monitors were

1 elevated compared to ambient levels, and equal to or lower than in-vehicle levels (e.g., Ott, 1994; Rodes

2 et al., 1999). A small portion of the CO concentrations inside a vehicle cabin comes from the vehicle

3 itself, while a substantial fraction comes from roadway traffic emissions entering the cabin via air

4 exchange. Studies summarized in the 2000 CO AQCD found that in-vehicle CO concentrations were

5 generally two to five times higher than ambient CO concentrations. High traffic volumes contributed to

6 increased in-vehicle concentrations.

7 Prior to the 2000 CO AQCD, it was well-known that CO levels in residences may be elevated

8 above ambient due to non-ambient indoor sources, such as cooking, space heating, and smoking.

9 Separation of indoor CO into ambient and non-ambient components is important for determining the

10 effect of ambient CO concentrations, although this has not been done successfully in previous studies.

11 Two large studies done in Denver, CO and Washington, DC in the early 1980s found that fixed-site

12 monitor concentrations were higher than personal exposures for those with low-level exposures, while

13 fixed site monitor concentrations were lower than exposures for those with high-level exposures (Akland,

14 1985; Johnson, 1984). Non-ambient sources contributing to high total exposures likely obscured this

15 relationship. In Denver, gas stove operation, passive smoking, and attached garages increased residential

16 indoor exposure by 2.6, 1.6, and 0.4 ppm respectively compared to individuals without those sources

17 present. Categorical analyses found significantly higher personal exposures on high ambient

18 concentration days than on low ambient concentration days, suggesting that personal exposures are

19 related to ambient levels. Non-ambient exposures tend to obscure the relationship between ambient CO

20 concentrations and personal exposure.

3.6.2. General Exposure Concepts

21 A general framework for human exposure modeling was described in the 2008 Draft PM ISA, 2008

22 NO_X ISA, and 2008 SO_X ISA (U.S. EPA, 2008e, f). A brief conceptual model of human exposure is

23 provided here with respect to CO for the readers' convenience. An individual's daily exposure to CO can

24 be described based on a compartmentalization of the person's activities over a time period of interest:

$$E = \int C_j dt$$

Equation 3-2

25 where E = exposure over some duration, C_j = CO concentration at location j, and dt = time spent in

26 location j. This basic equation can be broken down into a microenvironmental model that accounts for

27 exposure to CO of ambient (E_a) and non-ambient (E_{na}) origin of the form:

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

1   This assessment focuses on the ambient component of exposure because the non-ambient portion of

2   exposure is subject to individual behavior. Daily E_a can be expressed in terms of the fraction of time spent

3   outdoors and indoors being exposed to ambient CO concentration, C_a (Wilson et al., 2000):

$$E_a = \left(f_o + \sum f_i F_{inf_i} \right) C_a$$

4   where f = fraction of time, subscript o = outdoor, subscript i = indoor, and F_{inf} = infiltration factor. Finf

5   quantifies the equilibrium fraction of the CO concentration outside the microenvironment that penetrates

6   inside the microenvironment and remains in mixture. It is a function of the building air exchange

7   characteristics and the properties of the gas. Assuming steady state ventilation conditions, the infiltration

8   factor is a function of the penetration (P) of CO, the air exchange rate (a) of the microenvironment, and

9   the rate of CO loss (k) in the microenvironment; $F_{inf} = Pa/(a+k)$. Given that $k \rightarrow 0$ for CO, F_{inf} reduces to

10 P. Equation 3-4 is subject to the constraint $f_o + \Sigma f_i = 1$ to reflect the total exposure over a specified time

11 period. The indoor term has a summation because indoor exposure can occur in various

12 microenvironments throughout a time period of interest. "Outdoor" exposure can occur in parks, yards,

13 sidewalks, and on bicycles or motorcycles. "Indoor" refers to being inside any aspect of the built

14 environment, e.g., home, office buildings, enclosed vehicles (automobiles, trains, buses), and/or

15 recreational facilities (movies, restaurants, bars). The complex human activity patterns that dictate

16 exposure across the population (all ages) are illustrated in Figure 3-31 (Klepeis et al., 2001). This figure

17 illustrates the diversity of daily activities among the population as well as the proportion of time spent in

18 each microenvironment. Although activities in Klepeis et al. (2001) are presented over a day, information

19 from this figure can be extracted to deduce variation over a 1-h or 8-h period.

20   As seen in equation 3-4, ambient exposure is a linear function of the ambient CO concentration.

21 The ambient exposure factor, α, is the ratio between the personal exposure to ambient CO and the ambient

22 concentration of CO (or the ambient exposure factor); i.e., $\alpha = E_a/C_a$. α is therefore the proportionality

23 factor in equation 3-4, i.e., $\alpha = f_o + \Sigma f_i F_{inf_i}$ (α varies between 0 and 1). If a person's exposure occurs in a

24 single microenvironment, the ambient component of a microenvironmental CO concentration can be

25 represented as the product of the ambient concentration and F_{inf}. If there are no significant local outdoor

26 sources and sinks of CO, then C_a can be approximated by the concentration measured by an ambient

27 monitor. If local sources and sinks exist and are significant, then the ambient component of outdoor air

28 must be estimated using dispersion models, land use regression models, receptor models, fine scale

29 chemistry-transport models or some combination of these techniques.

1   A variety of approaches can be used to estimate exposure to ambient CO. In some cases, individual
2   personal exposures are measured with personal exposure monitors (PEMs), where personal samples are
3   taken to estimate population exposure. In other cases, ambient concentrations are used as an exposure
4   indicator. The ambient concentration may be based on measurements made at a single ambient monitor or
5   as the average of several ambient monitors.

6   Very few recent exposure assessment studies utilized measurements of CO concentration and none
7   of the recent exposure error studies used measurements of personal and ambient CO exposure data,
8   although Sheppard et al. (2005) presented a conceptual model for nonreactive pollutants that could
9   include CO. Many recent studies analyzing exposure error used PM data (e.g., Sheppard et al., 2005;
10   Wilson and Brauer, 2006; Zeger et al., 2000). The lack of recent CO data contributes to uncertainty
11   regarding personal-ambient relationships. However, review of exposure error studies for PM, under the
12   assumption that it is nonreactive, is instructive for discerning the relative influence of ambient and non-
13   ambient exposures if consideration is made for differences between CO and PM with respect to indoor
14   source variability and infiltration.

15   Wilson and Brauer (2006) showed significantly stronger associations between health effects and
16   ambient exposure than between health effects and total personal exposure. The use of personal exposure
17   in population exposure assessment studies could cause various errors in the health effect estimate because
18   the correlation between personal exposure and ambient concentration may be different for each subject in
19   a panel and may not be statistically significant (Wilson et al., 2007). The correlation between ambient
20   concentration and personal exposure may be high for some subjects, in which case the exposure error
21   caused by using ambient concentration instead of personal exposure may be small. In other subjects, the
22   correlation may be low or negative (and not statistically significant). In this case, the exposure error will
23   be high and may obscure relationships between ambient exposure and health effects. Differences in
24   correlation observed in these studies occurred in part because the ambient exposure factor, α, was
25   different for each subject. The relationships between ambient concentration and the ambient component
26   of personal exposure were statistically significant for all subjects. The analyses of Wilson and Brauer
27   (2006) and Wilson et al. (2007) focused on PM, which is subject to indoor-outdoor differences in size
28   distribution and chemical composition related to differential infiltration. However, this issue is still
29   relevant for CO because non-ambient CO exposure is uncorrelated with ambient CO exposure and
30   therefore could obscure health effects relationships observed in epidemiologic studies. Therefore, ambient
31   concentration is better than total personal exposure as an indicator of ambient CO exposure.
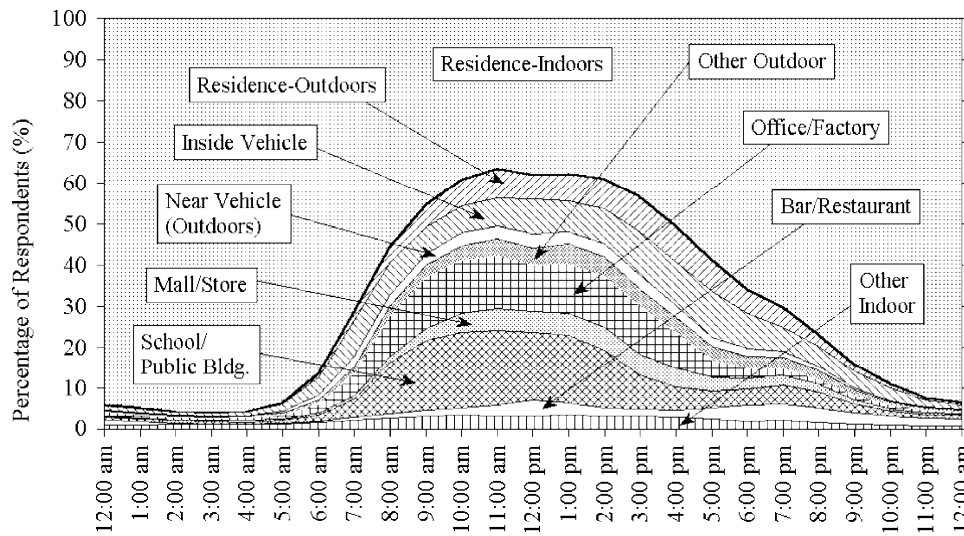
Source: Klepeis et al. (2001))

Figure 3-31.   Distribution of time that a sample population spends in various environments, from the National Human Activity Pattern Survey.

3.6.3. Monitoring Issues Associated with Exposure Assessment

3.6.3.1. Exposure Assessment using Community-Based Ambient Monitors

1   Instrumentation and associated monitoring errors are described in section 3.4; exposure error
2   related to instrumental measurement error in ambient monitors is described here. Because there will likely
3   be some random component to instrumental measurement error, the correlation of the measured CO
4   concentration with the true CO concentration will likely be less than 1. Sheppard et al. (2005) indicated
5   that instrument error in the individual or daily average concentrations have "the effect of attenuating the
6   estimate of α." However, Zeger et al. (2000) stated that the "instrument measurement error in the ambient
7   levels…is close to the Berkson type" and in order for this error to cause substantial bias in later estimation
8   of the health outcome, the error term (the difference between the true concentrations and the measured
9   concentrations) must be strongly correlated with the measured concentrations. Zeger et al. (2000)
10   suggested that, "Further investigations of this correlation in cities with many monitors are warranted."

3.6.3.2. Personal Exposure Monitors

11   Portable monitors for measuring personal CO exposure include the Langan and Draeger monitors,
12   both of which use electrochemical oxidation-reduction techniques (Langan, 1992). These monitors
13   continuously log CO concentrations, making them suitable for use in personal monitoring studies. More
14   detail on personal CO monitoring is provided in the 2000 CO AQCD (U.S. EPA, 2000).

Measurement Error in Personal Exposure Monitors

1   Personal electrochemical CO monitors are subject to interference and drift, and have a relatively

2   high detection limit (approximately 1 ppm) relative to current ambient concentrations. Previous studies in

3   the 1980's and 1990's, when ambient levels were higher, were able to successfully deploy these monitors,

4   but more recent exposure studies have avoided personal CO measurements due to the high percentage of

5   non-detects. The lack of a suitable personal monitor for measuring low-level exposures (<1 ppm) has

6   hampered field studies assessing personal exposure to ambient CO. Chang et al. (2001) evaluated the

7   Langan CO monitor as part of an air quality sampling manifold. At high (0.4-3.0 ppm) CO

8   concentrations, the instrument correlated well ($R^2 = 0.93$) with a reference CO monitor with the Langan

9   underestimating the CO concentration by 41%. When ambient levels fell consistently below that level,

10   coefficient of determination (R^2) between the Langan and reference monitor fell to $R^2 = 0.4$ in summer

11   and $R^2 = 0.59$ in winter with the arithmetic average concentration underestimated by 47% in summer and

12   by 63% in winter. Chang et al. (2001) pointed out the need for frequent instrument zeroing to minimize

13   instrument drift. Abi Esber et al. (2007a) evaluated a similar personal electrochemical CO sensor, the

14   GEM™ 2000, by comparing measured concentrations with those obtained through co-located grab bag

15   sampling in a vehicle cabin. Differences between the GEM™ 2000 and the reference samples were fairly

16   low during weekday driving (differences = 2.1-10.6%). Differences on Sundays, when traffic was

17   significantly lower than during weekdays, were dependent on vehicle ventilation conditions, with better

18   agreement when vehicle ventilation allowed for higher cabin CO concentrations (differences = 3.4-5.6%),

19   but the electrochemical sensor did not compare well with reference values when concentrations were low

20   (differences = 20-71%). In general, it is difficult to separate the large instrumental measurement error

21   seen at concentrations below instrument LOD from variation in non-ambient exposures. This large

22   variation in personal measurements can result in high levels of classical measurement error (Sheppard et

23   al., 2005).

3.6.4. Indoor/Outdoor Relationships and Infiltration

24   CO is a relatively inert gas, making the indoor decay rate negligible compared to typical air

25   exchange rates (~1/h). In the absence of indoor sources, this would lead to an indoor-outdoor

26   concentration ratio (I/O) of approximately 1. For this reason, few studies have measured I/O for CO.

27   Polidori et al. (2007) measured I/O of 0.94-1.21 for two retirement communities in the Los Angeles area.

28   The authors suggested that similarity between I/O for CO and NO_X can be attributed to lack of indoor

29   sources of either gas. Chaloulakou and Mavroidis (2002) reported I/O for CO measurements in the

30   absence of indoor sources in a school building in Athens, Greece and found that I/O varies with season.

31   During the summer, median I/O was reported to be 0.57 on weekdays, 0.91 on Saturdays, and 0.81 on

1 Sundays. In winter, median I/O was reported to be 0.82 during weekdays, 0.90 on Saturdays, and 0.74 on

2 Sundays. The authors attributed the lower weekday I/O values to traffic-based peaks in outdoor CO

3 concentrations that were not translated to indoors. In a related work, Chaloulakou et al. (2003) reported

4 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

5 (the presence of other sources was not clearly stated but assumed zero). However, observed indoor values

6 are often greater than outdoor concentrations in the presence of indoor sources. A recent study in the U.K.

7 reported I/O of 3.9-4.3 in homes with gas cookers (Dimitroulopoulou et al., 2006), which is consistent

8 with previous studies. A multipollutant study conducted in 2000-2001 attempted to measure I/O for CO

9 and calculated residential infiltration factors, but low CO concentrations resulted in a large number of

10 non-detects (Williams et al., 2003).

3.6.5. Personal/Ambient Relationships

3.6.5.1. Panel and Population Exposure Studies

11 Although several multi-pollutant exposure studies have been conducted recently in the U.S., (e.g.,

12 Sarnat, 2006), most have not included CO in the suite of pollutants, possibly due to limitations in personal

13 monitoring techniques. A few studies conducted in Europe and Canada measured personal-ambient

14 relationships for CO.

15 The EXPOLIS study (Georgoulis et al., 2002) found that 48-h personal exposures were

16 significantly correlated with ambient concentrations in each of five European cities (Athens, Basel,

17 Helsinki, Milan, and Prague). Controlling for source terms, including ETS, traffic, and natural gas

18 appliances, regression coefficients between personal exposure and ambient concentration ranged from

19 0.28 in Milan to 1.99 in Helsinki. Regression coefficients greater than 1 may indicate location of a fixed

20 site monitor away from local sources (e.g., roadways), resulting in a lower ambient value than

21 experienced in the urban core. As part of this study, personal CO exposure was measured for a panel of 50

22 office workers in Milan (Bruinen de Bruin et al., 2004). Average measured 1-h personal exposures were

23 7.3 ppm in comparison with 5.0 ppm for fixed site 1-h measurements. Average 8-h (3.3 ppm) and 24-h

24 (2.1 ppm) CO concentrations were the same for personal and fixed site measurements. Percentage of time

25 exposed, exposures, and percentage of exposure from the Bruinen de Bruin et al. (2004) study, in the

26 absence of non-ambient CO from ETS and gas cooking, are shown in Table 3-9. The largest percentage of

27 CO exposure was attributed to home indoor exposure in the absence of indoor sources, while the highest

28 exposure levels were observed during transit. Scotto di Marco et al. (2005) found similar results. Bruinen

29 de Bruin et al. (2004) and Scotto di Marco et al. (2005) found that mobile source emissions were

30 important contributors to personal exposure, as described in the following subsection.

Table 3-9. **Percentage of time exposed to ambient CO (adjusted to reflect the absence of non-ambient 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: Bruinen de Bruin et al. (2004).

1   EXPOLIS also looked at the special case of children's exposure to CO because children generally
2 do not produce CO in their daily activities and have no occupational exposures. Alm et al. (2000; 2001)
3 reported higher personal exposures than ambient concentrations for children aged 3-6 years old in
4 Helsinki. Their mean daily max 1-h exposure was 5.2 ppm, compared to 1.4 ppm measured at a fixed-site
5 monitor. For daily max 8-h and 24-h avg concentrations, the corresponding values were 2.9 ppm and
6 2.1 ppm for personal exposure and 0.8 and 0.6 ppm, respectively, for fixed site measurements. The
7 Spearman rank correlation, although statistically significant, was relatively low ($r = 0.15$) between
8 individual 24-h avg exposure and the ambient monitor. The correlation improved when the average
9 exposure of children measured on the same day ($r = 0.33$, 3-6 children) or the same week ($r = 0.55$, 10-23
10 children) was compared to the monitor data. A regression model using questionnaire data found that
11 parental smoking status, parental education, and presence of a gas stove explained 12% of the variability
12 in the 8-h max exposures, indicating that other factors, such as time spent outdoors and proximity to
13 roadways are likely to be important in determining personal exposure.
14   Kim et al. (2006) reported mean CO concentrations of 1.4 ppm for a panel of 28 cardiac-
15 compromised individuals in Toronto, Canada. Corresponding fixed-site monitor mean concentrations
16 ranged from 0.5-1.4 ppm, with an overall mean of 1.0 ppm. The observed higher personal exposures may
17 have been due to both indoor sources and proximity to roadways when outdoors. Personal-ambient
18 Spearman correlations ranged from -0.65 to 0.93, with a median of $r = 0.31$, indicating that while

1   moderate correlations are observed overall, inter-individual differences based on time spent in different
2   microenvironments have a strong influence on the observed correlation.
3   Lai et al. (2004) measured relationships between personal CO exposure and microenvironmental
4   (home indoor, home outdoor, and work indoor) concentrations in Oxford, U.K.. The highest personal
5   exposures were associated with smoking, cooking, and transportation while low correlations were
6   observed between personal and indoor residential concentrations, further indicating the importance of
7   indoor sources and the need to separate ambient contributions to personal exposure from total personal
8   exposure.

3.6.5.2. Commuting Time CO Exposure Studies

9   A number of studies focused on transit-time CO exposure, which can occur in a vehicle or while
10 walking or cycling. Kaur (2005) found that transit time exposures in London, U.K. were significantly
11 higher than measurements made at a fixed site background monitor away from traffic (0.3 ± 0.1 ppm) for
12 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),
13 and bus riders (0.8 ± 0.1 ppm). Curbside measurements (1.5 ± 0.7 ppm) in this study were slightly higher
14 than car riders' exposures. Duci et al. (2003) found that average in-transit concentrations were highest for
15 cars (winter: 21.4 ± 4 ppm), followed by pedestrians (winter: 11.5 ± 2.6 ppm; summer: 10.1 ± 1.7 ppm),
16 buses (winter: 10.4 ± 2.9 ppm; summer: 9.4 ± 3.6 ppm), trolley (winter: 9.6 ± 1.9 ppm; summer: $8.2 \pm$
17 3 ppm), and rail (winter: 4 ± 0.6 ppm; summer: 3.4 ± 0.7 ppm). Duci et al. (2003) did not provide fixed
18 site CO concentrations but stated that in-transit exposures were higher in each case. Additional analyses
19 from the EXPOLIS study indicated that on-road mobile source emissions were the most important source
20 of CO exposure for non-ETS-exposed subjects (Bruinen de Bruin et al., 2004; Scotto di Marco et al.,
21 2005). Scotto di Marco et al. (2005) found that, for a panel of 201 adult Helsinki residents (aged 25-55
22 years), subjects spent 8.1% of their time in transport, which accounted for 12.6% of their total exposure
23 (range of means = 0.96 ppm on a train – 2.8 ppm in a car). Similarly, in a panel study of 50 office
24 workers, Bruinen de Bruin et al. (2004) found that, in the absence of non-ambient sources, the subjects
25 spent 8.5% of their time in transit, which accounted for 16.8% of their total exposure, with 2.6% of time
26 spent in a car or taxi accounting for 7.2% of exposure (mean = 5.7 ppm). Commuting time was an
27 important predictor of exposure, such that subjects living in low CO concentration suburban areas and
28 commuting to work experienced higher levels than urban residents with short commute times.
29   Gómez-Perales et al. (2004; 2007) measured CO exposures on buses, mini-buses, and metro cars in
30 Mexico City, Mexico to be 12 ppm, 15 ppm, and 7 ppm, respectively. These values are higher than
31 CONUS measurements and those presented by Kaur et al. (2005), but the relative difference between the
32 minibus and bus exposures in the Gómez-Perales et al. (2004; 2007) study are similar to those seen for the
33 taxi-to-bus or car-to-bus comparisons in Kaur et al. (2005). Alm et al. (1999) reported in-vehicle CO

1 concentrations of 5.7 ppm in the morning and 3.1 ppm in the afternoon commute for Kuopio, Finland.

2 Abi Esber et al. (2007b) report results from CO concentration measurements taken within an automobile

3 in Beirut, Lebanon during the morning commute period of 7:30 to 9:30 a.m. Weekday trip CO levels

4 ranged from 10.8 ppm with the windows open and vents closed to 37.4 ppm when driving with windows

5 and vents closed. Mean and standard deviation for ambient CO concentrations, obtained using a roadside

6 monitor in Beirut during the periods September-December 2003, August-September 2004, and

7 May-August 2005 were 1.4 ± 0.7, 1.6 ± 0.4, and 1.1 ± 0.7 ppm, respectively.

8 Abi Esber and El-Fadel (2008) compared the amount of CO produced by an automobile, driving

9 the same route of Beirut described in Abi Esber et al. (Abi Esber et al., 2007b) above, by sampling CO

10 directly from the engine of the vehicle and separately from the cabin of the car under three different

11 ventilation conditions. For the case when one window was half-open and vents were closed, engine CO

12 concentrations averaged 12.6 ppm while in-vehicle concentrations averaged 17.7 ppm, which was a

13 40.5% increase. With windows closed and the air conditioner operating on "recirculating air" mode, CO

14 concentrations averaged 13 ppm from the engine and 30.2 ppm in the vehicle cabin, a 132% increase.

15 With windows closed and the air conditioner on "fresh air" mode, engine CO concentrations averaged

16 18.3 ppm while in-vehicle concentrations were 20.5 ppm, which was only a 12% increase. Figure 3-32

17 shows that the time series for the cabin and engine CO samples are very similar for the fresh air scenario,

18 but for the recirculating air ventilation the concentration increases as a logarithmic-type function as CO

19 builds up in the cabin of the vehicle.
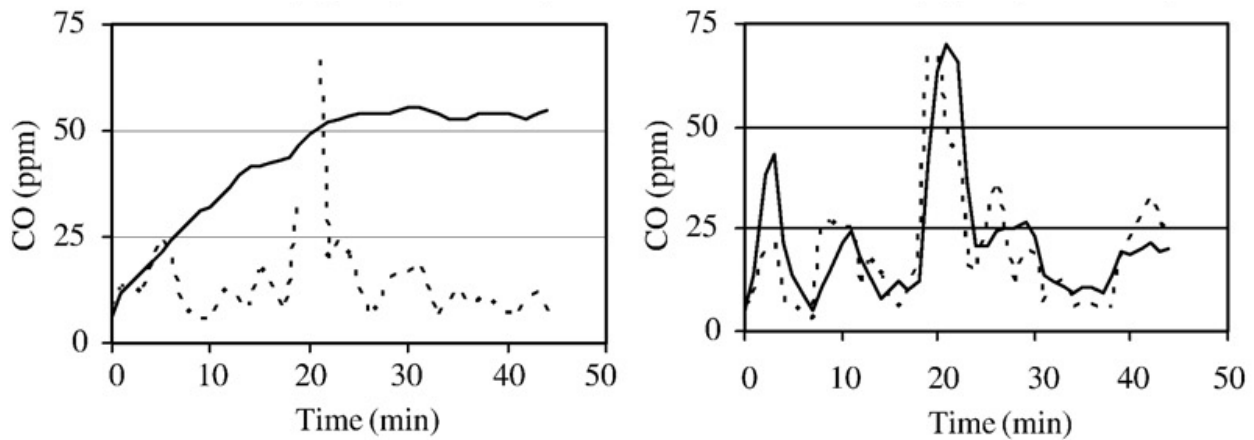
Source: Abi Esber and El Fadel (2008)

Figure 3-32. **Comparison of in-vehicle (solid line) and engine (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.**

1   Riedeker et al. (2003) measured CO concentrations inside patrol cars during shifts. Troopers
2   recorded in a time-activity diary the ventilation settings of their cars and exit/entry from the vehicle, and
3   the air conditioning was typically set to recirculation mode during the shifts. Riedeker et al. (2003) found
4   that CO concentrations (mean, SD: 2.6 ± 1.1 ppm) were higher than ambient monitor concentrations
5   (0.8 ± 0.3 ppm). They were also higher than roadside CO concentrations (1.1 ± 0.3 ppm), indicating that
6   either the vehicle itself contributes to in-cabin CO, or on-road concentrations are higher than roadside
7   concentrations, or both. Riedeker et al. (2003) noted that within-shift variability was higher than between-
8   shift variability, which underscores the variability in police officers' activities during a given shift. No
9   data was segregated by ventilation settings. Chang et al. (2000) measured CO concentrations during a
10   scripted activity study in Baltimore, MD in 1998 and 1999. Mean 1-h CO concentrations were near the
11   1 ppm detection limit of the Langan CO monitor. Microenvironmental CO concentrations were
12   significantly correlated with concentrations measured at a fixed-site ambient monitor for residential, other
13   indoor, in-vehicle, and outdoor near-road microenvironments during the winter. Significant correlations
14   were observed only for residential microenvironments during the summer. The location of the ambient
15   monitor near a roadway may have contributed to the lack of correlation with concentrations measured at
16   outdoor locations away from roadways. Microenvironmental concentrations inside vehicles were
17   significantly higher than those for other microenvironments.

18   Several factors may affect commuters' exposures. Van Wijnen et al. (1995) observed that while
19   bicycling, cyclists inhale 2.3 times as much air as pedestrians and drivers so that this group may, in fact,
20   inhale the most CO. Likewise, in their review of roadway exposures to CO and PM, Kaur et al. (2007)
21   listed a number of uncontrolled factors that may influence exposure. Vertical CO concentration gradients
22   have been documented with concentrations decreasing with height; lower breathing zone height among
23   children may make them more likely to be exposed to higher CO concentrations. With respect to
24   transportation, Kaur et al. (2007) suggested that vehicle ventilation, speed, position in traffic, and
25   start/stop activity influence in-vehicle exposures. Gómez-Perales et al. (2007) also noted that meteorology
26   can impact in-vehicle exposures, with evening increases in wind speed causing a 50% reduction in CO
27   exposures among bus and minibus commuters. Alm et al. (1999) made a similar observation in a study of
28   urban commuters' exposure within a vehicle.

29   Studies of vehicle self-pollution are instructive for considering potential for ambient CO infiltration
30   in vehicles. Behrentz et al. (2004) used sulfur hexafluoride (SF_6) tracer gas emitted from school bus
31   engines to determine the proportion of in-vehicle pollution related to self-pollution. Based on the SF_6
32   concentration, they calculated that 0.04-0.29% of the bus cabin air contained exhaust for high emitting
33   diesel engines, 0.01-0.03% for "regular" diesel buses, 0.02-0.04% for buses fitted with a particle trap, and
34   0.03-0.04% for buses running on compressed natural gas. SF_6 concentrations were higher when bus
35   windows were closed.

3.6.5.3. CO Exposure Assessment Variability and Error

1   In the context of determining the effects of ambient pollutants on human health, the association
2   between the ambient component of personal exposures and ambient concentrations is more relevant than
3   the association between total personal exposures (ambient component + non-ambient component) and
4   ambient concentrations. If there are no non-ambient sources of a pollutant, the total personal exposure is
5   equal to the ambient personal exposure. However, non-ambient sources could significantly affect personal
6   exposures to CO. Unlike PM, CO has no chemical identifiers that can be used to apportion ambient and
7   non-ambient sources of CO (other than radioactive isotopes, whose detection is rare). For the general U.S.
8   population, exposure error analysis for epidemiologic studies indicates that fixed-site measured ambient
9   CO concentration is generally a good indicator of ambient exposure to CO, as discussed in more detail
10   below.
11   Figure 3-33 shows hourly vs. personal CO concentration data obtained by Chang et al. (2000) for a
12   1998-1999 multi-pollutant sampling campaign in Baltimore, MD. Personal exposures were obtained in
13   five separate microenvironments in this study. A high degree of scatter is evident in this figure, which
14   suggests that these personal exposures are influenced by both ambient and non-ambient sources of CO.
15   Figure 3-34 is a box plot of the personal-to-ambient CO concentration ratio for the same five
16   microenvironments. Figure 3-34 shows that personal exposures in vehicles were on average 2.8 times
17   higher than ambient during the summer and 4.1 times higher than ambient in the winter. For the other four
18   microenvironments tested, the average ratio was around 1. Wide variability is seen in these plots,
19   particularly during the summer. Much of that variability could be due to the influence of non-ambient
20   sources, which would then result in poor correlation between total personal exposure and ambient
21   concentration.
22   Zeger et al. (2000) stated that there are three error terms in the estimate of a person's exposure: 1)
23   error from using pooled population data in lieu of individual data, 2) error between total exposure and
24   ambient concentration, and 3) error between the actual and measured ambient concentration. Zeger et al.
25   (2000) also described that errors related to individual variability and measurement (as stated above for the
26   latter) are of the Berkson type and therefore not expected to bias estimates of exposure or health effects.
27   Moreover, Sheppard et al. (2005) simulated ambient and non-ambient exposures to a non-reactive
28   pollutant and observed that non-ambient CO exposure has no effect on the association between ambient
29   CO exposure and health outcomes for the case where ambient and non-ambient sources were
30   independent.
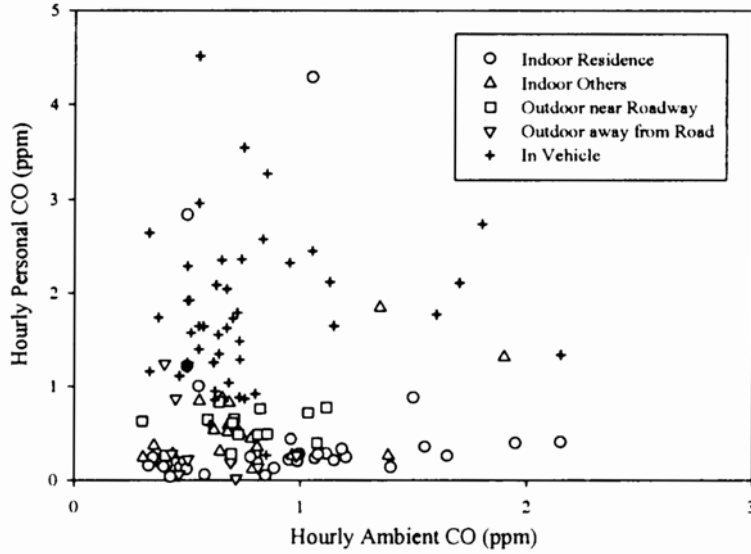
Source: Chang et al. (2000)

Figure 3-33. Hourly personal vs. ambient CO concentrations obtained in Baltimore, MD. Summer of 1998 in five settings: indoor residence, indoor other, outdoor near road, outdoor away from road, in vehicle.
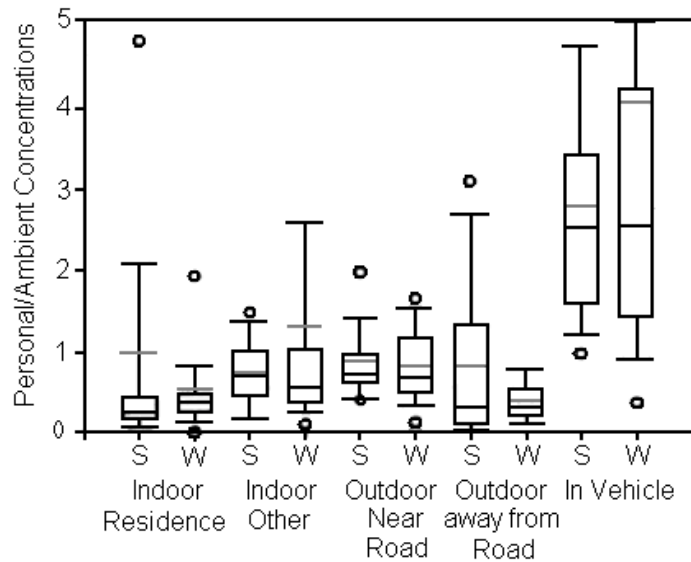
Source: Adapted from Chang et al. (2000)

Figure 3-34. Box plots of the ratio of personal to ambient concentrations obtained in Baltimore, MD. Summer of 1998 and winter of 1999 in five settings: indoor residence, indoor other, outdoor near road, outdoor away from road, in vehicle. The dotted line shows the mean, and the solid line shows the median. S = summer; W = winter.

1   For community time-series epidemiology, the community averaged concentration, not the

2   concentration at each fixed monitoring site, is the concentration variable of concern (Zeger et al., 2000).

3   The correlation between the concentration at a central community ambient monitor and the community

4   averaged concentration depends on at least the following three factors. First, the distribution of monitors

5   across space: CO emissions from traffic might show spatial heterogeneity near roadway sources but have

6   a more homogeneous distribution farther downwind. It follows that use of a large number of samplers will

7   dampen inter-sampler variability. Second, the relationship between the measurement at the ambient

8   monitoring site and the community average concentration: if the site is selected to measure a "hot spot" or

9   pollution from a nearby source, estimates of community exposure could be skewed upwards. Third,

10   terrain features or source location: different terrain features or source locations across sub-communities

11   may differ in the temporal pattern of pollution. Intra-urban spatial heterogeneity was discussed in detail in

12   Section 3.5.1.2. Community exposure may not be well-represented when monitors cover large areas with

13   several sub-communities having different sources and topographies. For example, with the exception of

14   two closely located samplers, there is poor inter-sampler correlation among the Pittsburgh, PA CO

15   samplers. This variability reflects the wide topographical differences throughout the Pittsburgh CSA as

16   well as variation in traffic usage and distance to near-road sources at each point in contrast to the Phoenix

17   CBSA, where inter-sampler correlation was high.

18   Epidemiologic studies of long-term exposure rely on differences among communities in long-term

19   average ambient concentrations. If exposure errors are different in the different communities, the

20   differences in long-term ambient concentrations among communities may not represent the differences in

21   long-term average exposures. For example, there may be community to community differences in

22   measurement error, in the average ambient exposure factor (α) or the average non-ambient exposure. This

23   could happen if exposure to newly formed pollutants generated by vehicular traffic or pollutants from

24   other localized sources differed among the spatial areas. Thus, in a regression of health effects against

25   average concentration (as an indicator for average exposure) there could be a different amount of error

26   (either positive or negative) in the exposure indicator for each spatial area. This could add error and bias

27   the slope up or down. Geostatistical tools enable the use of concentration fields that include spatial

28   variations in concentration. However, it has not yet been possible to include individual or small-area

29   variations in the personal exposure to ambient concentrations or variations in personal exposures to

30   indoor-generated pollutants in long-term studies of the associations of pollutants with health effects.

3.6.6. Multi-pollutant Exposures

31   Since incomplete combustion is the primary source of ambient CO, exposure to ambient CO is

32   accompanied by exposure to other combustion-related pollutants, such as NO_X and PM. Thus, ambient

1   CO is often considered a surrogate for exposure to traffic-generated pollutants. However, the specific mix

2   of CO with NO_X and PM depends on the source; for example, the mixture generated by gasoline engines

3   differs from that produced by gas combustion. Correlations between ambient CO and ambient $PM_{2.5}$,

4   PM_{10}, NO_2, SO_2, and O_3 from AQS data and the peer-reviewed literature were presented in section 3.5.3.

5   Nationwide ambient CO was most highly correlated with ambient NO_2 followed by $PM_{2.5}$ and PM_{10}.

6   Correlations between CO and $PM_{2.5}$ were not always statistically significant on a national basis;

7   correlations were insignificant for ambient CO with ambient SO_2 and ambient PM_{10}, and ambient CO was

8   negatively correlated with ambient O_3. Correlations of ambient CO with $PM_{2.5}$ and PM_{10}, were much

9   higher and more statistically significant at some of the select cities, as shown in Annex A.

10   Sarnat et al. (2001) analyzed the relationship between personal exposure to $PM_{2.5}$ and ambient CO

11   concentrations and found significant associations during winter of ambient CO with personal exposure to

12   total $PM_{2.5}$ (slope = 3.99) and to ambient $PM_{2.5}$ (slope = 6.30). Ambient CO was not significantly

13   associated with personal $PM_{2.5}$ exposure during summer. Sarnat et al. (2005) also reported significant

14   association between ambient CO concentrations and personal $PM_{2.5}$ exposure for winter (three 12-day

15   sessions in 2000, dates not specified) only and significant year-round associations between ambient CO

16   concentrations and personal exposure to SO_4^{2-} aerosols.

17   Relationships between personal CO exposures and copollutants were reported less frequently in the

18   literature, but results from these studies were consistent with the findings cited above. In a study of

19   personal exposures to CO, $PM_{2.5}$, and ultrafine PM in a street canyon, Kaur et al. (2005) found low

20   Pearson's correlation of personal CO exposure with personal $PM_{2.5}$ exposure (r = 0.23). Personal CO

21   exposure had much better correlation with personal ultrafine PM exposure (r = 0.68). Chang et al. (2000)

22   reported correlations of personal CO exposure with personal $PM_{2.5}$, personal toluene, and personal

23   benzene exposures in Baltimore, MD at five locations, labeled indoor residential, indoor nonresidential,

24   outdoors near roadway, outdoors away from road, and in vehicle. Much variability was observed in the

25   correlations for different locations and seasons (winter vs. summer). In general, the correlations tended to

26   be stronger and more significant in the winter. Chang et al. (2000) pointed out that indoor air exchange

27   rates tend to be lower in winter, which could cause these correlations to be more sensitive to non-ambient

28   sources. Significant associations of CO with benzene and toluene were observed in-vehicle. Because CO

29   exposures most often occur together with exposure to other combustion-related pollutants, interpretation

30   of health studies using ambient CO data can be a challenge, as discussed further in Chapter 5.

3.6.7. Exposure Modeling

31   A number of modeling techniques to describe air pollutant exposures at the individual and

32   population level have been published since 2002. Ambient CO exposure models often assume that

1 vehicular traffic is the sole source of emissions given that roughly 90% of urban CO is estimated to come
2 from traffic (Gulliver and Briggs, 2005). Individual-level models can predict personal exposure based on
3 a person's path of travel and on conditions of the surrounding environment using traffic and meteorology
4 data. One such example is the Space-Time Exposure Modeling System (STEMS) (Gulliver and Briggs,
5 2005). Population-based methods, such as the Air Pollution Exposure (APEX) model
6 (www.epa.gov/ttn/fera/human_apex.html), Stochastic Human Exposure and Dose Simulation (SHEDS)
7 (Burke et al., 2001), and EXPOLIS models (Kruize et al., 2003), involve stochastic treatment of the
8 model input factors. Another approach is to predict location-based exposures using a deterministic model
9 such as the CMAQ model, California Line Source Dispersion Model (CALINE), CALPUFF (long-range
10 plume transport model), or Operational Street Pollution Model (OSPM) for determination of street-level
11 pollution coupled with infiltration models to represent indoor exposure to ambient levels (Appel et al.,
12 2008; Gilliam et al.; Hering, 2007; Mensink and Cosemans, 2008; Wilson and Zawar-Reza, 2006).
13 Stochastic and deterministic methods are often combined, as described below. Land use regression (LUR)
14 models have also been developed to describe pollution levels as a function of geographic source behavior
15 (Gilliland et al., 2005; Ryan and LeMasters, 2007; Veen et al., 1997). Similarly, other spatial interpolation
16 techniques have been used to determine geographic distributions of exposure (Marshall et al., 2008).
17 Compartmental models, such as the Indoor Air Model (INDAIR), can be used to assess exposure to
18 infiltrated ambient air pollutants in a deterministic or probabilistic framework (Dimitroulopoulou et al.,
19 2001; 2006). A detailed description of various modeling techniques is provided in the 2008 NO_X ISA and
20 2008 SO_X ISA annexes (2008f, g), and an explanation of associated modeling errors is provided in the
21 2008 Draft PM ISA (U.S. EPA, 2008f). Applications of these models to assessment of CO exposure are
22 described in the following paragraphs.
23   The STEMS model maps exposures based on inputs for traffic levels, atmospheric dispersion,
24 background concentrations, and geography. Gulliver and Briggs (2005) tested the STEMS model for CO
25 and observed some correlation between modeled and measured CO concentrations ($R^2 = 0.41$), which was
26 consistent with results for PM_{10} and NO_X. Exposures were estimated from the predicted ambient CO
27 concentration using a term similar to α that varied depending on whether the individual was walking or in
28 a vehicle. Gulliver and Briggs (2005) noted that a limitation to modeling CO is the scarcity of background
29 CO data obtained at rural sites. For this reason, they assumed a constant value obtained from estimates
30 made over the North Atlantic Ocean. Although the authors only presented detailed results for a model of
31 PM_{10} based on traffic and meteorology in Northampton, U.K., they found that the majority of variation on
32 a given day in modeled exposure among school children was due to differences in travel routes. Variation
33 across days was also influenced by background and meteorological conditions. Similar results can be
34 expected for CO based on the tendency for variation of the CO concentration profile on the neighborhood
35 and micro-scales (Jerrett et al., 2004). Flachsbart (Flachsbart) tested numerous meteorological, traffic, and
36 background CO input variables in a regression approach to predicting CO exposure among individuals

1   while traveling in a vehicle. This work showed travel time and average speed of on-road vehicles to be
2   important determinants of CO exposure in a vehicle. Results from individual models of this nature can be
3   pooled to develop a distribution for examination of population effects or for comparison with population
4   exposure models.
5   Bruinen de Bruin et al. (2004) utilized the EXPOLIS model to predict CO population exposures in
6   Milan, Italy. The simulation results showed that the U.S. 8-h NAAQS level was exceeded in one case out
7   of 1,000. The model also showed that exposures exceeded 20 ppm in one case out of 100,000. The results
8   were not shown to be very sensitive to the number of microenvironments (e.g., outdoors, indoors, in
9   vehicle) included in the model. The probabilistic NAAQS Exposure Model for CO (pNEM/CO) was used
10   in the 1992 and 2000 CO AQCDs (U.S. EPA, 1992, 2000) to estimate personal CO exposures among
11   adult populations. Given reductions in ambient CO levels, details, and results from those efforts are
12   provided here. The current version of this model, now known as APEX, was used for exposure
13   assessment in the O_3 NAAQS review (U.S. EPA, 2006b).
14   To examine indoor concentrations of ambient CO, Dimitroulopoulou et al. (2006) used the
15   probabilistic formulation of the INDAIR model to examine indoor exposure to ambient CO, along with
16   NO_X and PM for a given distribution of background CO levels, meteorology, residential air exchange rate,
17   and residential room dimensions. They found that 24-h avg CO concentration increased from 1.86 ppm
18   outdoors to 1.90-1.93 ppm indoors in the absence of non-ambient sources, and that indoor 24-h avg CO
19   concentration could increase to 1.93-2.00 ppm in the presence of smoking and to 1.98-2.32 ppm in the
20   presence of gas cooking. Similarity between the outdoor and non-source indoor concentrations was
21   attributed to the lack of CO loss mechanisms. With maximum CO concentrations modeled at 3.3 ppm in
22   the absence of sources, the probability density function of indoor exposure to ambient fell well below the
23   8-h NAAQS. In the Reducing Urban Pollution Exposure from Road Transport (RUPERT) study, Bell et
24   al. (2004) presented methodology to use the probabilistic form of INDAIR for development of personal
25   exposure frequency distributions of CO, NO_X, and PM based on time spent in residential, transportation,
26   school, office, and recreational environments with inputs from transportation source categories (Chen et
27   al., 2008).
28   Another set of approaches to improve exposure estimates in urban areas involves construction of a
29   concentration surface over the geographic area. This does not estimate exposure directly because it does
30   not account for activity patterns or concentrations in different microenvironments. It provides an
31   improved estimate of the expected local outdoor concentration near residences, schools or workplaces,
32   and roadways across the area. There are two main types of approaches: spatial interpolation of measured
33   concentrations, and regression models using land use, roadway characteristics, and other variables to
34   predict concentrations at receptors in the domain. Rigorous first-principles models, such as dispersion
35   models and chemical transport models, can also be used for this type of application, but are less suitable
36   because they have intensive resource requirements and are typically applied over larger domains.

1   Marshall et al. (2008) compared four spatial interpolation techniques for estimation of CO
2   concentrations in Vancouver, BC. The investigators assigned a daily average CO concentration to each of
3   the 51,560 postal code centroids using one of the following techniques: (1) the concentration from the
4   nearest monitor within 10 km, (2) the average of all monitors within 10 km, (3) the inverse-distance-
5   weighted (IDW) average of all monitors in the area, and (4) the IDW average of the three closest monitors
6   within 50 km. Method 1 (the nearest-monitor approach) and Method 4 (IDW-50 km) had similar mean
7   and median estimated annual average concentrations, although the 10th-90th percentile range was smaller
8   for IDW-50. This is consistent with the averaging of extreme values inherent in IDW methods. The
9   Pearson correlation coefficient between the two methods was 0.88. Methods 2 and 3 were considered sub-
10   optimal and were excluded from further analysis. In the case of method 2, a single downtown high-
11   concentration monitor skewed the results in the vicinity, partially as a result of the asymmetric layout of
12   the coastal city of Vancouver. Method 3 was too spatially homogenous, because it assigned most locations
13   a concentration near the regional average, except for locations immediately adjacent to a monitoring site.
14   LUR results were also reported in this study for NO and NO_2, and indicated that LUR's higher spatial
15   precision reflects neighborhood-scale effects from nearby land use, but may not account for urban-scale
16   variation. These results highlight the variation in local concentration estimates with choice of estimation
17   technique.

3.7. Summary and Conclusions

3.7.1. Sources of CO

18   In the U.S., on-road mobile sources constituted more than half of total CO emissions in 2002, or
19   ~63 MT of ~109 MT total. In metropolitan areas in the U.S., for example, as much as 70-75% of all CO
20   emissions can come from on-road vehicle exhaust (U.S. EPA, 2006a). The majority of these on-road CO
21   emissions derive from gasoline-powered vehicles since the O2 content, pressure, and temperature
22   required for diesel fuel ignition do not produce large quantities of CO. Anthropogenic CO emissions are
23   estimated to have decreased 35% between 1990 and 2002. On-road vehicle sector emissions controls have
24   produced nearly all these national-level CO reductions. Nationally, biogenic emissions, excluding fires,
25   were estimated to contribute ~5% of total CO emissions from all sources in 2002, and fires in 2002 added
26   another 13%, or ~14.5 MT, to the national CO emissions total.

3.7.2. Physics and Chemistry of Atmospheric CO

1   CO is produced by photooxidation of CH_4 and other VOCs in the atmosphere. Estimating the CO

2   yield from oxidation of HCs larger than CH_4 requires computing the yields of several intermediate

3   products and reactants from oxidation of the parent molecules. The major pathway for removal of CO

4   from the atmosphere is reaction with OH to produce CO_2 and HO_2. The mean photochemical lifetime (τ)

5   of CO in the northern hemisphere is ~57 days. During winter at high latitudes, CO has nearly no

6   photochemical reactivity on urban and regional scales.

3.7.3. Ambient CO Measurements

7   As of March 2008, 19 automated FRMs and no FEMs had been approved for CO. All EPA FRMs

8   for CO operate on the principle of nondispersive infrared (NDIR) detection and can include gas filter

9   correlation (GFC). The required lower detection limit for FRMs in the EPA network is 1.0 ppm. In 2007,

10   there were 285 CO monitors meeting the 75% completeness requirements and reporting values year-

11   round to the AQS in the 50 states, plus the District of Columbia, Puerto Rico, and the Virgin Islands. At

12   least 70 monitors across the U.S. have been positioned at microscale within 10 m of a road to capture

13   near-road concentrations. At larger scales, monitor distance from a road is inversely related to the road's

14   average daily traffic count to capture community averages.

3.7.4. Environmental CO Concentrations

15   CO concentration data for 1-h and 8-h intervals were available for 243 counties and autonomous

16   cities or municipalities that maintained active CO monitoring stations meeting the 75% completeness

17   criteria for the years 2005-2007. There were no violations of the 1-h or 8-h NAAQS in those years. The

18   nationwide mean, median, and interquartile range for 1-h measurements reported between 2005-2007

19   were 0.5, 0.4, and 0.4 ppm, respectively, and these statistics did not change by more than 0.1 ppm for

20   each year of the 3-year period. The nationwide mean, median, and interquartile range for 8-h daily max

21   concentrations reported between 2005-2007 were 0.7, 0.5, and 0.5 ppm, respectively. The 2006 annual

22   second highest 8-h CO concentration averaged across 144 monitoring sites nationwide was 75% below

23   that for 1980 and is the lowest concentration recorded during the past 27 years. The mean annual second

24   highest 8-h ambient CO concentration has been below 5 ppm since 2004. The downward trend in CO

25   concentrations in the 1990s parallels the downward trend observed in CO emissions and can be attributed

26   largely to decreased mobile source emissions.

27   The correlation structures for measurements at the monitors in each of the 11 CSAs/CBSAs

28   examined for this assessment reveal a wide range of response between monitors in each city and among

1   the cities judged against each other. While this wide range is produced by the interactions of many

2   physical and chemical elements, the location of each monitor and the uniqueness of its immediate

3   surroundings can often explain much of the agreement or lack thereof. CO concentrations can be elevated

4   near roadways and decrease with increasing distance from the road. Likewise, micro- and neighborhood-

5   scale variation related to urban topography or microenvironmental source distribution may have a

6   significant effect on ambient CO concentrations with respect to street canyon concentrations. Anchorage,

7   AK had concentrations roughly twice those of the other metropolitan areas. Most of the CSAs/CBSAs

8   examined here had diel concentration curves with pronounced morning and evening rush hour peak CO

9   levels, although diel CO concentrations had less variability for New York City, Atlanta, and Seattle than

10   for the other eight cities. For most metropolitan areas examined here, concentrations were generally

11   highest in the winter (December-February) and fall (September-November) and decreased, on average,

12   during the spring (March-May) and summer (June-August). Measurements near or below the required

13   FRM lower detection limit of 1.0 ppm coupled with the coarsely reported measurement resolution

14   (0.1 ppm) can artificially influence the comparison statistics shown in the tables and result in apparent

15   heterogeneity in the box plots (Figures 3-13 through Figures 3-16).

16   For nationwide copollutant correlation data, ambient CO had the highest mean and median

17   correlations with ambient NO_2, followed by $PM_{2.5}$ (correlations vary by season). The SO_2 and PM_{10}

18   correlations did not appear to be statistically significantly different from zero for any season, and

19   statistical significance was only observed in winter and fall for $PM_{2.5}$. Correlations between CO and NO_2

20   were significant for all seasons but summer. Correlations between CO and O_3 were significant and

21   negatively correlated for winter only. The copollutant correlation plots shown in Annex A illustrate higher

22   and more statistically significant correlations between CO and PM in several but not all of the select cities

23   displayed.

24   This assessment has used data from 2005-2007 at 12 remote sites as part of the international CCGG

25   CASN in the CONUS, Alaska, and Hawaii to determine PRB. All sites demonstrate the well-known

26   seasonality in background CO with minima in the summer and fall and maxima in the winter and spring.

27   The 3-year avg CO PRB in Alaska was 130 ppb; in Hawaii it was 99 ppb; and over the CONUS it was

28   132 ppb.

3.7.5. Exposure Assessment and Implications for Epidemiology

29   Very few recent exposure assessment studies involve CO concentration data. The studies of

30   personal exposure to CO presented here generally found that the largest fraction of an individual's

31   exposure to ambient CO occurs indoors but the highest CO exposure levels occur in transit. Among

32   commuters, exposures were highest for those traveling in automobiles in comparison with those traveling

1 in buses and motorbikes and with those cycling or walking. A portion of that exposure is thought to come

2 from the vehicle in which the exposed person travels. Commuting time was an important predictor of

3 exposure, such that subjects living in low-CO concentration suburban areas and commuting to work

4 experienced higher CO levels than residents of higher-CO concentration urban areas with short commute

5 times. Additional analyses indicated that on-road mobile emissions were the most important source of CO

6 exposure for non-ETS-exposed subjects. Results have also indicated that time spent outdoors and

7 proximity to roadways may have been important in determining personal exposure in children.

8 Uncontrolled factors that may influence exposure include vertical CO concentration gradients; vehicle

9 ventilation, speed, position in traffic, and start/stop activity; and meteorology.

10   For the general U.S. population, exposure error analysis for epidemiologic studies indicates that

11 fixed-site measured ambient CO concentration is generally a good indicator of ambient exposure to CO.

12 Errors associated with exposure to non-ambient CO sources, for example smoking or gas cooking, are of

13 the Berkson type and therefore not expected to bias estimates of exposure or health effects. Simulations of

14 ambient and non-ambient exposures to a non-reactive generic pollutant demonstrated that non-ambient

15 exposure had no effect on health effects outcomes for the case where ambient and non-ambient sources

16 were independent. Likewise for community time-series epidemiology, selected monitoring sites are

17 thought to be representative of community averages. Measurement at a "hot spot" could skew community

18 exposure estimates upward. Topographical or source variability could produce differences in the temporal

19 pattern of pollution. Differences such as those produced by variation in local sources among communities

20 in long-term exposure studies may also produce error in estimation of the ambient exposure factor. Such

21 differences could add error, and therefore influence the slope of health effects estimate regressions up or

22 down.

23   Several studies have examined multi-pollutant exposure. Since incomplete combustion is the

24 primary source of ambient CO, exposure to ambient CO is accompanied by exposure to other

25 combustion-related pollutants, such as NO_X and PM. High correlations of ambient CO with NO_2 and

26 $PM_{2.5}$ have been observed in the peer-reviewed literature and AQS data. Thus, ambient CO is often

27 considered a surrogate for exposure to traffic-generated pollutants. Because CO exposures most often

28 occur together with exposure to other combustion-related pollutants, interpretation of health studies using

29 ambient CO data can be a challenge, as discussed further in Chapter 5.

Chapter 4. Dosimetry and Pharmacokinetics of Carbon Monoxide

4.1. Introduction

1   Inhaled ambient CO elicits various health effects by binding with and altering the function of a

2   number of heme-containing molecules, mainly Hb. Traditional concepts for CO pathophysiology have

3   been based on the high affinity of CO for deoxyhemoglobin, resulting in COHb formation and consequent

4   reduction in O_2-carrying capacity of blood and impaired O_2 delivery to tissues. Research on the basics of

5   CO pharmacokinetics date back to the 1890s, but since the late 1970s has become limited. Current

6   literature primarily focuses on endogenous CO produced by the metabolic degradation of heme by heme

7   oxygenase (HO) and its role as a gaseous messenger. This chapter reviews the physiology and

8   pharmacokinetics of CO. The chapter draws heavily from Chapter 5 of the previous AQCD (U.S. EPA,

9   2000). Relevant new data are included when available. New explanations of recent models of Hb binding

10   are included, as well as discussion on tissue CO concentrations using new methods of extraction.

11   CO binds with a number of heme-containing molecules including Mb and cytochromes, but none

12   have been studied as extensively as Hb. The primary focus of this chapter is placed on the models and

13   kinetics of such binding and the factors influencing this event. The chapter discusses effects at ambient or

14   near ambient levels of CO leading to low COHb levels ($\leq 5\%$); however few studies are available at

15   ambient CO concentrations. Both human and animal studies using higher CO exposure concentrations,

16   resulting in moderate to high COHb levels (<20%), are discussed where needed to understand CO

17   kinetics, pathophysiologic processes, and mechanisms of cytotoxicity. Where human studies could not

18   experimentally test certain hypotheses or were unavailable, animal experiments were used as surrogates.

19   CO uptake and elimination has been shown to be inversely proportional to body mass over

20   environmentally relevant exposure levels, meaning the smaller the animal, the faster the rate of absorption

21   and elimination (Klimisch et al., 1975; Tyuma et al., 1981). However, the basic mechanisms of CO

22   toxicity between experimental animals and humans are similar and are thus extrapolated from animals to

23   humans in this chapter, keeping in mind a number of interspecies differences.

4.2. Carboxyhemoglobin Formation

4.2.1. The Coburn-Forster-Kane and Other Models

1   Investigators have modeled the effect of CO binding to Hb in a number of ways. Empirical and
2   mechanistic models are two distinct approaches that have been taken to model in vivo COHb formation
3   after CO exposure. First, empirical models were used to predict COHb by regressing concentration and
4   duration of exogenous CO exposure with COHb. These methods were reviewed in depth in the previous
5   AQCD (U.S. EPA, 2000). These models are limited to estimating COHb in the exact conditions on which
6   the models were based. These simple models include those by Peterson and Stewart (1970) and Ott and
7   Mage (1978), as well as various others (Selvakumar et al., 1992; Singh et al., 1991). Using these simple
8   models, it was shown that the presence of brief ambient CO concentration spikes averaged over hourly
9   intervals may lead to underestimating the COHb concentration by as much as 21% of the true value. To
10   avoid this problem, it was suggested that ambient CO measurements be monitored and averaged over 10–
11   15 minute periods (Ott and Mage, 1978).
12   Secondly, mechanistic models use physical and physiological processes and an understanding of
13   biological processes to predict COHb production. The most commonly used mechanistic method for
14   predicting levels of blood COHb after CO inhalation is the Coburn-Forster-Kane equation or CFK model
15   developed in 1965 (Coburn et al., 1965). This differential equation was developed to examine endogenous
16   CO production, using the major physiological and physical variables influencing this value. Since then, it
17   has been shown to provide a good approximation to the COHb level at a steady level of inhaled
18   exogenous CO (Peterson and Stewart, 1975; Stewart et al., 1973b). The CFK model describes a four-
19   element, physical system containing an exogenous CO source, a transfer interface, an endogenous CO
20   source, and a storage compartment. The linear CFK model assumes O_2Hb concentration is constant and is
21   as follows in Equation 4-1:

$$V_b \frac{d[COHb]_t}{dt} \;=\; \dot{V}_{CO} - \frac{[COHb]_0\, P_{\bar{C}}O_2}{[O_2Hb]M} \left(\frac{1}{\dfrac{1}{D_L CO} + \dfrac{P_B - 47}{\dot{V}_A}} \right) + \left(\frac{P_I CO}{\dfrac{1}{D_L CO} + \dfrac{P_B - 47}{\dot{V}_A}} \right)$$

Equation 4-1

22   where V_b is blood volume in milliliters (mL); $[COHb]_t$ is the COHb concentration at time t in mL CO/mL
23   blood, at standard temperature and pressure, dry (STPD); $\dot{V}_{CO}$ is the endogenous CO production rate in
24   mL/min, STPD; $[COHb]_0$ is the COHb concentration at time zero in mL CO/mL blood, STPD; $[O_2Hb]$ is
25   the O_2Hb concentration in mL O_2/mL blood, STPD; M is the Haldane coefficient representing the CO

1   chemical affinity for Hb; $P_{\bar{C}}O_2$ is the average partial pressure of O_2 in lung capillaries in mmHg; $\dot{V}_A$ is

2   the alveolar ventilation in mL/min, STPD; D_LCO is the lung diffusing capacity of CO in mL/min/mmHg,

3   STPD; P_B is the barometric pressure in mmHg; and P_ICO is the CO partial pressure in inhaled air in

4   mmHg.

5   This model assumes instant equilibration of COHb concentration between venous and arterial

6   blood, gases in the lung, and COHb concentrations between blood and extravascular tissues, which is not

7   physiologically representative. The nonlinear CFK equation incorporates the interdependence of COHb

8   and O_2Hb levels since they are derived from the same pool of blood Hb. The nonlinear equation is more

9   physiologically accurate; however the linear CFK equation gives a good approximation to the nonlinear

10   solution over a large range of values during CO uptake and during low levels of CO elimination (Smith,

11   1990). The linear equation prediction of COHb concentration at or below 6% will only differ ± 0.5% from

12   the nonlinear equation prediction. Sensitivity analysis of the CFK equations has shown that alterations in

13   each variable of the equation will affect the outcome variably at different times of exposure (McCartney,

14   1990). Figure 4-1 illustrates the temporal changes in fractional sensitivities of the principal physiological

15   determinants of CO uptake for the linear form of the CFK equation, where TH_b is the total blood

16   concentration of Hb in g Hb/mL blood and F_ICO is the fractional concentration of CO in ambient air

17   in ppm. The fractional sensitivity of unity means that, for example, a 5% error in the selected variable

18   induces a 5% error in the predicted COHb value by the nonlinear model. As Figure 4-1 demonstrates, a

19   constant or given percent error in one variable of the model does not generally produce the same error in

20   the calculated blood COHb, and the error is time dependent. Thus, each variable influencing CO uptake

21   and elimination will exert its maximal influence at different times of exposure.
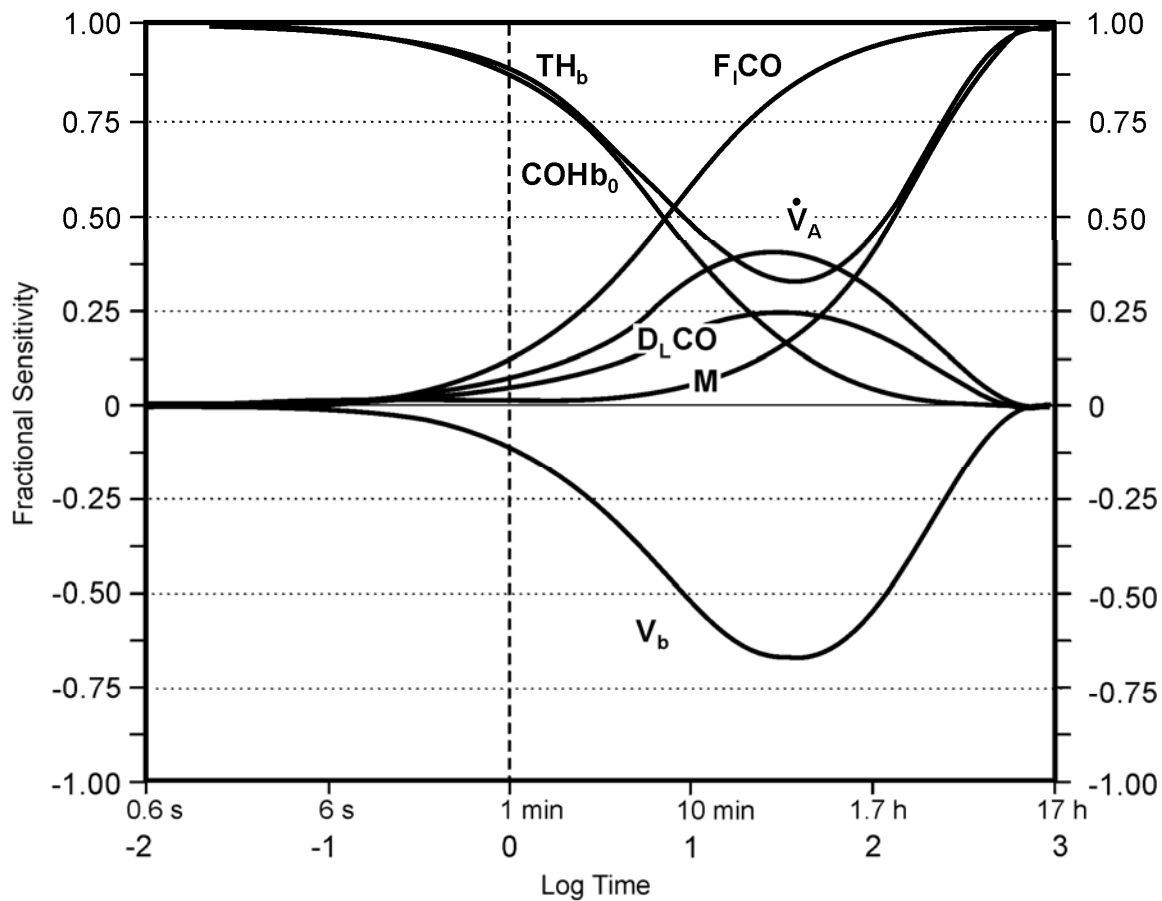
Figure 4-1.   Plot of fractional sensitivities of selected variables versus time of exposure.

1   The mechanistic CFK model contains a number of assumptions under which the model is solely

2   applicable, including 1) ventilation is a continuous process, 2) equilibrium between plasma CO

3   concentration and COHb concentration is obtained in the pulmonary system, 3) percent COHb can exceed

4   100% saturation in the linear model, and 4) it does not account for the shape of the O_2 or CO saturation

5   versus pO_2 or pCO relation (McCartney, 1990). Estimations outside of these assumptions have been

6   attempted but with less predictive agreement. For example, transient exposures such as those that would

7   simulate everyday conditions would violate the assumption of a single, well-mixed vascular compartment.

8   COHb levels during exposure of subjects exposed to frequent but brief high CO exposures (667 to

9   7,500 ppm for 75 s to 5 min) were not accurately predicted by CFK modeling (Benignus et al., 1994;

10   Tikuisis et al., 1987a; Tikuisis et al., 1987b). Consistently, the predicted COHb value overpredicted

11   venous COHb (0.8 to 6%) and underpredicted arterial COHb (1.5 to 6.1%) and this disparity increased

12   after exercise. Individual differences between arterial and venous COHb varied from 2.3 to 12.1%

13   (Benignus et al., 1994). These inaccuracies between measured and predicted COHb values disappeared

14   after simulated mixing of arterial and venous blood and thus are likely due to delays in mixing of arterial

1 and venous blood and differences in cardiac output and lung wash-in. A modified CFK was created to

2 adjust for these issues and produce a more accurate COHb prediction (Smith et al., 1994).

4.2.2. Multicompartment Model

3   In addition to the limitations discussed above, the CFK model does not account for extravascular

4 storage sites for CO, such as muscle Mb. CO will undergo reversible muscle Mb binding, similar to Hb,

5 as well as uptake into other extravascular tissues (Vreman et al., 2006). A five compartment model has

6 been proposed to predict CO uptake and distribution from acute inhalation exposure and contains

7 components for lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue (Bruce and Bruce,

8 2003; Bruce et al., 2008; 2006). This model structure is illustrated in Figure 4-2. This model includes the

9 dynamics of CO storage in the lung and its dependence on ventilation and CO pressure of mixed venous

10 blood, relaxes the assumption Hb is saturated by including the role of CO in altering the O_2 dissociation

11 curve, includes a subcompartmentalized muscle tissue compartment, accounts for dissolved CO in blood

12 and tissue, and predicts COHb based on age and body dimensions. This multicompartment model is

13 limited by its exclusion of cellular metabolism or Mb diffusion, simplification of within tissue bed spatial

14 variability, and assumes ventilation and P_AO_2 are constant. This model better predicts COHb levels when

15 inspired CO levels change rapidly or when incomplete blood mixing has occurred, and better predicts the

16 CO washout time course compared to the CFK equation. Bruce and Bruce (2003) compared the two

17 models and found similar results for long term exposure settings (1,000 min), however, the

18 multicompartment model predicted somewhat lower COHb levels compared to the CFK model over

19 transient CO uptake conditions when using data taken from Peterson and Stewart (1970).
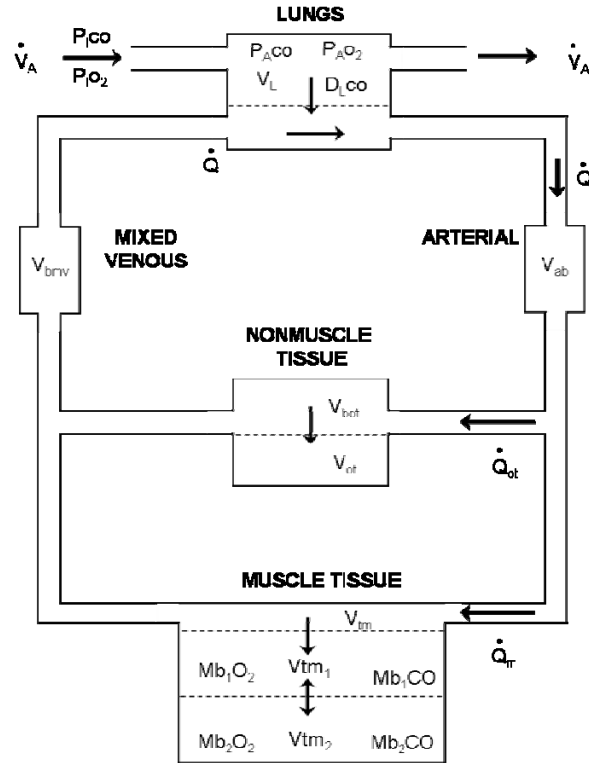
Source: Modified from Bruce et al. (2008)

Figure 4-2.   **Overall structure of the 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.**

4.2.3. Mathematical Model Usage

1   Since measurements of COHb in the population are not readily available, mathematical models are

2   used to predict the resulting COHb levels from various CO exposure scenarios. Figure 4-3 illustrates the

3   predictions of COHb after 1, 8, 12, or 24 h of CO exposure at a range of concentrations in a healthy,

4   inactive, adult human. The Quantitative Circulatory Physiology (QCP) model, which integrates human

5   physiology using over 4,000 variables and equations based on published biological interactions, was used

6   to predict these values (Abram et al., 2007; Benignus et al., 1987; 2006). This dynamic model uses the

7   nonlinear CFK equation with modifications presented in Smith et al. (1994). The data in Figure 4-3 are

8   presented as the change in percent COHb from endogenous due to CO exposure to NAAQS relevant

9   levels from 0-35 ppm (A) and relevant ambient levels from 0-6 ppm (B). Endogenous CO production

10   varies as described in Section 4.5 but generally results in less than 1% COHb, with a QCP modeled value

11   of 0.39% at time zero. Figure 4-3 illustrates that 35 ppm CO for 1 h results in an increase of 0.56% COHb

12   over endogenous levels and 9 ppm CO for 8 h results in a 0.83% increase over endogenous levels. Also,

1   these graphs show that long term, low concentration CO exposure results in equivalent COHb levels to
2   higher concentration, acute exposure. For example, COHb resulting from 35 ppm for 1 h (0.56%) is
3   approximately equivalent to 6 ppm for 8 h (0.55%) or 4 ppm for 24 h (0.57%).
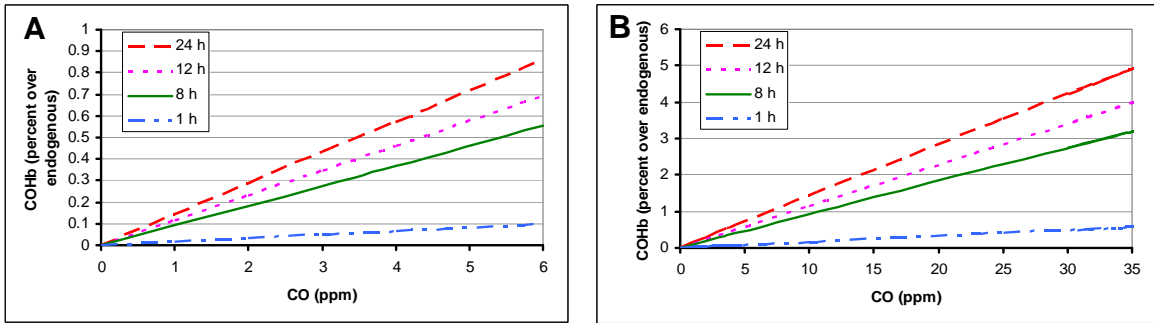
Figure 4-3.   Predicted COHb increments over endogenous levels resulting from 1, 8, 12, and 24 h CO exposures in a modeled healthy human at rest. The QCP model used a dynamic nonlinear CFK with affinity constant M = 230. The data are presented as the change in percent COHb from endogenous levels due to CO exposure to 0-6 ppm (A) and 0-35 ppm (B). Note: Graph A is a subset of Graph B.

4.3. Absorption, Distribution, and Elimination

4.3.1. Pulmonary Absorption

4   Pulmonary uptake of CO accounts for all environmental CO absorption and occurs at the
5   respiratory bronchioles and alveolar ducts and sacs. CO and O_2 share various physico-chemical
6   properties, thus allowing for the extension of the knowledge about O_2 kinetics to those of CO despite the
7   differences in the reactivity of the gases. The exchange of CO between the air and the body depends on a
8   number of physical (e.g., mass transfer and diffusion), as well as physiological factors (e.g., alveolar
9   ventilation and cardiac output), which are controlled by environmental conditions, physical exertion, and
10 other processes discussed in Section 4.4. The ability of the lung to take up inhaled CO is measured by
11 D_LCO, and CO uptake (V_{CO}) representing the product of D_LCO and the mean alveolar pressure (P_ACO).
12 The importance of dead space volume, gas mixing and homogeneity, and ventilation/perfusion matching
13 were discussed in depth in the 2000 AQCD (U.S. EPA, 2000).

4.3.1.1. Mass Transfer of Carbon Monoxide

1   Mass transfer refers to the molecular and convective transport of CO molecules within the body
2   stores, driven by random molecule motion from high to low concentrations. CO enters through the airway
3   opening (mouth and nose) and transfers in a gas phase to the alveoli. CO transport is due to convective
4   flow, the mechanical action of the respiratory system, and diffusion in the acinar zone of the lung (Engel,
5   1983). Then, CO diffuses in a "liquid" phase across the air-blood interface, binding red blood cell (RBC)
6   Hb. At environmental CO levels, CO uptake into RBC is limited by the reaction rate of binding of CO to
7   O_2Hb forming COHb. Pulmonary capillary RBC CO diffusion is rapidly achieved (Chakraborty et al.,
8   2004; Gibson and Roughton, 1955; Reeves and Park, 1992; Roughton and Forster, 1957). The rate and
9   level of COHb depends upon the pCO, pO_2 in the air, time of exposure, and the ventilation rate (Roughton
10 and Forster, 1957). Most of the body CO is bound to Hb; however, 10-15% of the total body CO is
11 located in extravascular tissues primarily bound to other heme proteins (Coburn, 1970a). Considerable
12 concentrations of CO have been measured in spleen, lung, kidney, liver, muscle, and heart (Vreman et al.,
13 2005; Vreman et al., 2006), whereas less CO is localized to fatty tissues, such as adipose and brain (Table
14 4-1). The transfer of CO occurs by a partitioning of CO between Hb and tissue. Less than 1% of the total
15 body CO stores appear as dissolved in body fluids, due to the insolubility and small tissue partial pressure
16 of CO (Coburn, 1970a). Transport pathways and body stores of CO are shown in Figure 4-4.

Table 4-1a.   CO concentration in pmol/100 g ww tissue – human.

Exposure	Adipose	Brain	Muscle	Heart	Kidney	Lung	Spleen	Blood	% COHb
Background	2 ± 1	3 ± 3	15 ± 9	31 ± 23	23 ± 18	57 ± 59	79 ± 75	165 ± 143	1.5 ± 1.2
Fire	5 ± 4	7 ± 5	24 ± 16	54 ± 33	27 ± 11	131 ± 127	95 ± 69	286 ± 127	3.8 ± 3.2
Fire + CO	18 ± 29	17 ± 14	168 ± 172	128 ± 63	721 ± 427	1097 ± 697	2290 ± 1409	3623 ± 1975	40.7 ± 28.8
CO asphyxiation	25 ± 27	72 ± 38	265 ± 157	527 ± 249	885 ± 271	2694 ± 1730	3455 ± 1347	5196 ± 2625	56.4 ± 28.9

Source: Vreman et al. (2006)

Table 4-1b.   CO concentration in pmol/mg fresh weight – adult mouse.

Exposure	Brain	Muscle	Heart	Kidney	Lung	Spleen	Liver	Intestine	Testes	Blood	% COHb
Background	2 ± 0	10 ± 1	6 ± 1	7 ± 2	3 ± 1	6 ± 1	5 ± 1	4 ± 2	2 ± 1	45 ± 5	0.5
500 ppm CO	18 ± 4	14 ± 1	100 ± 18	120 ± 12	250 ± 2	229 ± 55	115 ± 31	9 ± 7	6 ± 3	2648 ± 400	28
30 µM heme	2 ± 0	7 ± 1	14 ± 3	7 ± 2	8 ± 3	11 ± 1	8 ± 3	3 ± 1	2 ± 0	88 ± 10	0.9
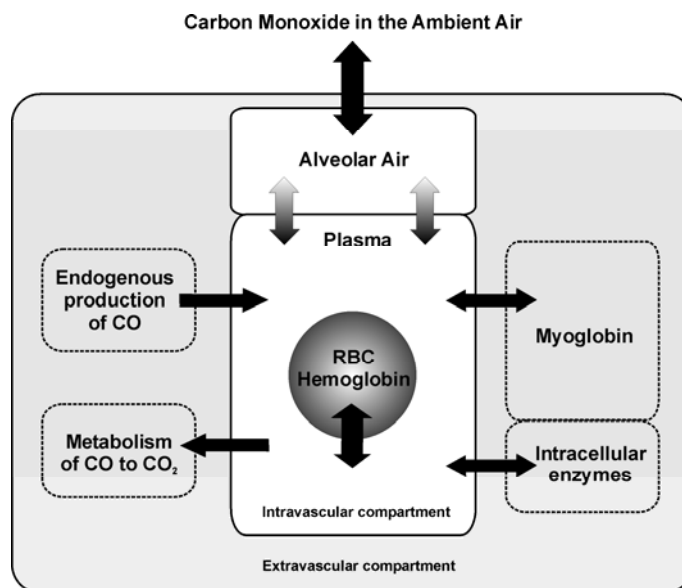
Figure 4-4.   Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.

4.3.1.2. Lung Diffusion of Carbon Monoxide

1   Lung diffusion of CO is an entirely passive process of gas diffusion across the alveolo-capillary

2   membrane, through the plasma, across the RBC membrane and into the RBC stroma, where CO binding

3   to Hb rapidly occurs. Membrane and blood phase transfer are governed by physico-chemical laws,

4   including Fick's first law of diffusion. The diffusing capacity of the lung for CO, represented as D_LCO, is

5   a measurement of the partial pressure difference between inspired and expired CO. Due to the rapid

6   binding of CO to Hb, a high pressure differential between air and blood exists when CO air levels are

7   increased. Inhalation of CO-free air reverses the pressure differential (higher CO pressure on the blood

8   side than the alveolar side), and then CO is released into the alveolar air. Since CO is also produced

9   endogenously, CO release will also be affected by this production pressure. However, the air-blood

1 gradient for CO is usually higher than the blood-air gradient; therefore, CO uptake will be a

2 proportionately faster process than CO elimination.

3   A number of factors have been found to affect D_LCO including Hb concentration, cardiac output

4 ($\dot{Q}$), erythrocyte flow, COHb concentration, P_ACO_2, body position, exercise, time of day, age, etc.

5 (Forster, 1966; Hsia, 2002). D_LCO consistently decreases after intense bouts of exercise, likely due to the

6 redistribution of blood volume to the periphery (Hanel et al., 1997; Manier et al., 1991). However, in

7 going from rest to exercise D_LCO can increase linearly from: lung expansion leading to unfolding and

8 distension of alveolar septa, opening and/or distension of capillaries as $\dot{Q}$ increases, increased capillary

9 hematocrit, and more homogeneous distribution of capillary erythrocytes (Hsia, 2002). D_LCO is less

10 dependent upon lung volume at mid-range vital capacity, but at extreme volumes the diffusion rate is

11 varied, higher than average at total lung capacity and lower at residual volume (McClean et al., 1981).

4.3.2. Tissue Uptake

4.3.2.1. The Respiratory Tract

12   The upper respiratory tract contributes little to the overall COHb uptake. The lung has nearly

13 constant exposure to CO; however, relatively little CO diffuses into the tissue except for at the alveolar

14 region en route to the circulation. No detectable uptake of CO was observed in the human nasal cavity or

15 upper airway (Guyatt et al., 1981) or in the monkey oronasal cavity after high CO exposure (Schoenfisch

16 et al., 1980).

4.3.2.2. The Blood

17   The blood is the largest reservoir for CO, where it reversibly binds to Hb. The chemical affinity of

18 CO for adult human Hb is approximately 218 times greater than that of O_2, meaning one part CO and 218

19 (210-250) parts O_2 would form equal parts of O_2Hb and COHb (Engel et al., 1969; Rodkey et al., 1969;

20 Roughton, 1970). This would happen when breathing air containing 21% O_2 and 960 ppm CO. This

21 concept was presented by Haldane and Smith (1898) and later represented as the Haldane constant M

22 (210-250) in the Haldane equation by Douglas, Haldane, and Haldane (1912). M is relatively unaffected

23 by changes in physiological pH, CO_2, temperature, or 2,3-diphosphoglycerate:

24

$$COHb \div O_2Hb = M \times (pCO \div pO_2)$$

<div align="right">Equation 4-2</div>

1   The Hb association rate for CO is 10% slower than O_2 and occurs in a cooperative manner
2   (Chakraborty et al., 2004; Sharma et al., 1976). Hb is composed of four globin chains each containing a
3   heme group capable of binding CO or O_2. The associative reaction rates become faster with successive
4   heme binding, attributed to interactions within the protein and to strains imposed on the heme and its
5   ligands (Alcantara et al., 2007). More simply, the greater the number of heme sites bound to CO, the
6   greater the affinity of free heme sites for O_2, thus causing Hb to bind and retain O_2 that would normally be
7   released to tissues. Cooperativity is greatly reduced in CO dissociation, but the rate of dissociation of CO
8   from Hb is orders of magnitude slower than O_2 ($k_{CO} = 4 \times 10^{-4} k_{O2}$), which accounts for the high affinity
9   values (Chakraborty et al., 2004). The half-time of dissociation reaction is about 11 seconds at 37 °C
10 (Holland, 1970). In general, CO uptake to COHb equilibrium is slower in humans and large animals,
11 requiring 8-24 h, than in smaller species such as rats, which will equilibrate in 1-2 h (Penney et al., 1988).
12   CO binding to Hb also has effects on the O_2 dissociation curve of the remaining Hb by shifting the
13 curve progressively to the left and altering the normal S-shaped curve to become more hyperbolic due to
14 increased cooperative O_2 binding (Roughton, 1970). This is referred to as the "Haldane effect" and causes
15 tissues to have more trouble obtaining O_2 from the blood, even compared to the same extent of reduced
16 Hb resulting from anemia. For example, Figure 4-5 (as explained in the 2000 AQCD) illustrates that an
17 acute anemia patient (50% of Hb) at a venous pO_2 of 26 mmHg (v'$_1$), 5 vol % of O_2 (50% saturation) was
18 extracted from the blood. In contrast, a CO poisoned person with 50% COHb, the venous pO_2 will have to
19 drop to 16 mmHg (v'$_2$) to release the same 5 vol % O_2. This more severe effect on O_2 pressure may lead
20 to brain O_2 depletion and loss of consciousness if any higher demand of O_2 is needed (e.g., exercise).
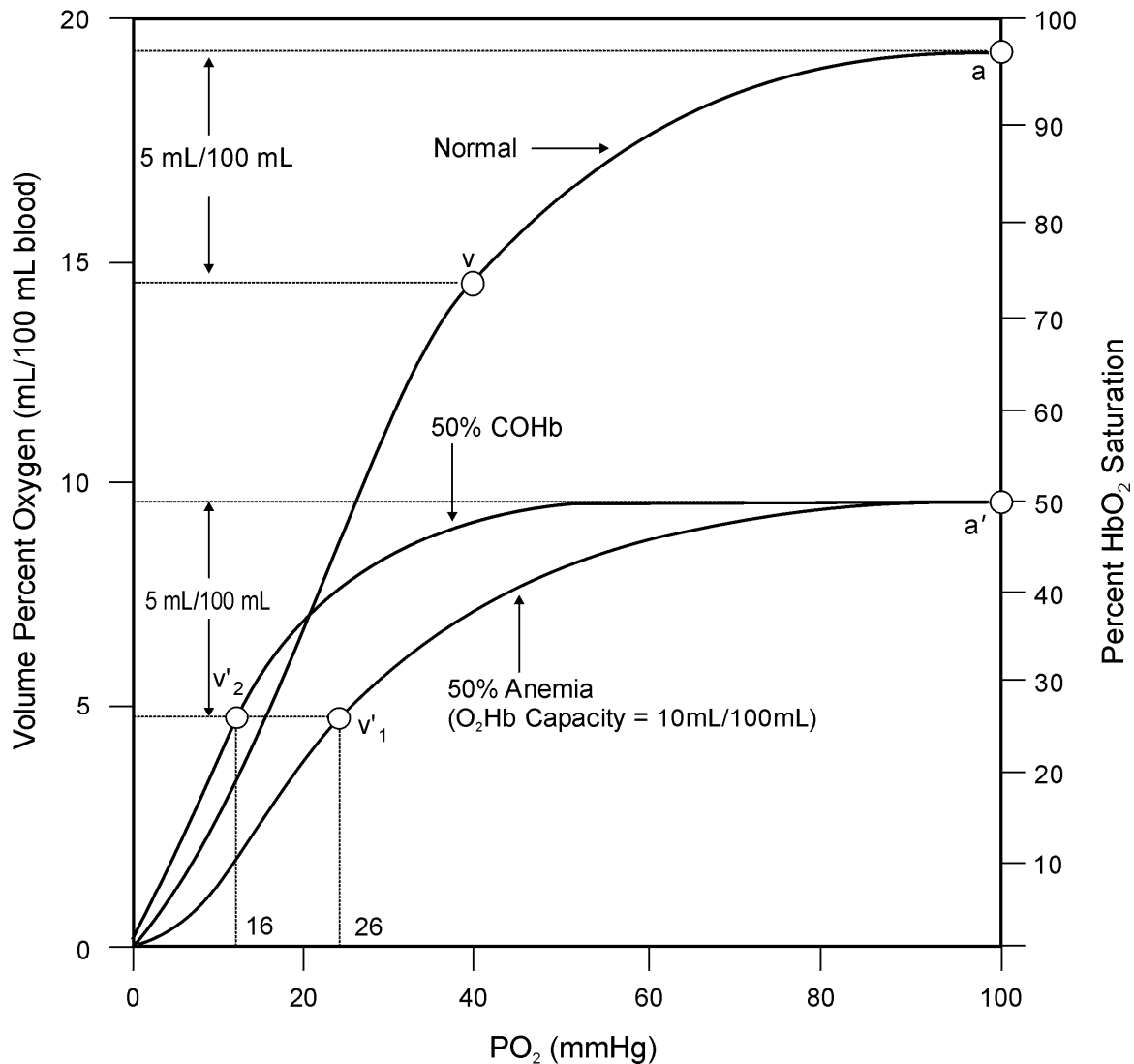
Figure 4-5. O₂Hb dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia.

4.3.2.3. Heart and Skeletal Muscle

1   Mb is a globular heme protein that facilitates O_2 diffusion from the muscle sarcoplasm to

2   mitochondria, acting as an O_2 supply buffer to maintain adequate pO_2 for mitochondria when the O_2

3   supply changes, as in exercise. O_2 has a greater affinity for Mb than Hb, which allows small changes in

4   tissue pO_2 to release large amounts of O_2 from O_2Mb (Wittenberg et al., 1975). Small reductions in O_2

5   storage capacity of Mb, due to CO binding, may have a profound effect on the supply of O_2 to the tissue.

6   Like Hb, Mb will undergo reversible CO binding, however the affinity constant is approximately

7   eight-times lower than Hb (M = 20-40 versus 218, respectively) (Haab, 1990). The association rate

1 constant of CO and Mb is approximately 27 times lower than O_2, however the dissociation rate constant is
2 approximately 630 times lower than O_2 (Gibson et al., 1986) causing CO to be retained and possibly
3 stored in the muscle. CO levels have been measured in human muscle and heart tissues with less than 2%
4 COHb concentrations at background levels averaging 15 and 31 picomole (pmol) CO/100 grams ww,
5 respectively (Vreman et al., 2006). Under conditions of CO asphyxiation, tissue concentrations increased
6 to 265 and 527 pmol CO/100 grams ww muscle and heart tissue, respectively; however, heart tissue
7 concentrations varied widely between individuals (See Table 4-1a). The capacity for diffusion of CO into
8 the muscle is represented by the coefficient D_mCO and is generally larger in males than in females, likely
9 due to the differences in muscle mass and capillary density (Bruce and Bruce, 2003). COMb
10 concentrations in the heart and skeletal muscle increase with work load, causing an increase in
11 COMb/COHb that is not as greatly seen at rest (Sokal et al., 1984). Subjects with 2% COHb, but not
12 those with 20% COHb levels, showed a significant uptake of CO from the blood to the muscle with
13 increasing work intensity of the quadriceps muscle (Richardson et al., 2002).

4.3.2.4. Other Tissues

14 CO binds with other hemoproteins, such as cytochrome P450, cytochrome *c* oxidase, catalase, and
15 peroxidase, but the possibility of this binding influencing CO-O_2 kinetics has not been established. CO
16 transfers between COHb and tissue, the extent of which varies between organs. Blood to tissue flux
17 causes less CO to be expired following CO exposure than what is lost from the blood in terms of COHb
18 (Roughton and Root, 1945). This value is estimated to be 0.3-0.4% min^{-1} or 0.24 mL/min (Bruce and
19 Bruce, 2003; Prommer and Schmidt, 2007). The equilibration rate from blood to tissue is controversial.
20 Newly modeled CO trafficking kinetics shows that CO continues to be taken up by the muscle and
21 extravascular tissues well beyond the end of exposure because of a less than instant equilibration (Bruce
22 and Bruce, 2006). Tables 4-1a and 4-1b contain tissue CO concentrations from human and mouse under
23 different CO exposure conditions. The distribution of CO between the different organs was shown to
24 follow the same pattern versus percent of the blood CO concentration, irrespective of the level of blood
25 CO (Vreman et al., 2006). These results are in conflict with older papers suggesting that negligible
26 retention of CO occurs in the liver or brain (Sokal et al., 1984; Topping, 1975).

4.3.3. Pulmonary and Tissue Elimination

27 Blood COHb concentrations are generally considered to have a monotonically decreasing, second-
28 order (logarithmic or exponential) elimination rate from equilibrium. However, more recent reports have
29 presented evidence for a biphasic washout curve, especially after short-term CO exposure (Figure 4-6)
30 (Bruce and Bruce, 2006; Shimazu et al., 2000; Wagner et al., 1975). This event is modeled by a two-

1 compartment system where the initial rapid decrease is the washout rate from the blood, followed by a

2 slower phase due to CO flux from the muscle and extravascular compartments back to the blood. Tissue

3 elimination rates have been reported as slower than those for blood (Landaw, 1973). The biphasic curve is

4 more obvious after short-term CO exposure (less than 1 h), whereas long-term CO exposure (5 h or more)

5 results in a virtually monoexponential elimination, which could account for the historical findings.

6 However, this elimination curve also follows a biphasic curve with a slightly higher rate of elimination

7 initially (Shimazu et al., 2000). Differences in elimination kinetics could also be a result of the variation

8 in CO exposure duration (Weaver et al., 2000).

9 The elimination of COHb is affected by a number of factors, including duration of exposure, P_aO_2,

10 minute ventilation, the time post-exposure for analysis due to extravascular stores, as well as inter-

11 individual variability (Bruce and Bruce, 2006; Landaw, 1973; Shimazu, 2001). The elimination rate does

12 not seem to be dependent upon the CO exposure source (e.g., fire, non-fire CO exposure) (Levasseur et

13 al., 1996). In addition, in a series of poisoned patients, the COHb elimination half-life was not influenced

14 by gender, age, smoke inhalation, history of loss of consciousness, concurrent tobacco smoking, degree of

15 initial metabolic acidosis (base excess), or the initial COHb level (Weaver et al., 2000). COHb

16 elimination half-life falls as the fractional inspired O_2 concentration increases. While breathing air at sea

17 level pressure, the expected half-life in adult males is approximately 285 minutes, but may be shorter in

18 adult females. With inhalation of normobaric 40% O_2, the half-life falls to 75 minutes and futher to 21

19 minutes when breathing 100% O_2 because of greater competition for Hb by O_2 (Landaw, 1973). Another

20 study reports the half-life falls to 74 minutes (mean) after breathing 100% O_2, although the range in this

21 particular study was 26 to 148 minutes (Weaver et al., 2000). In addition, COHb half-life will fall further

22 after normocapnic hyperoxic hyperpnea (i.e., hyperventilation while maintaining normal CO_2 pressure in

23 high O_2) (Takeuchi et al., 2000).
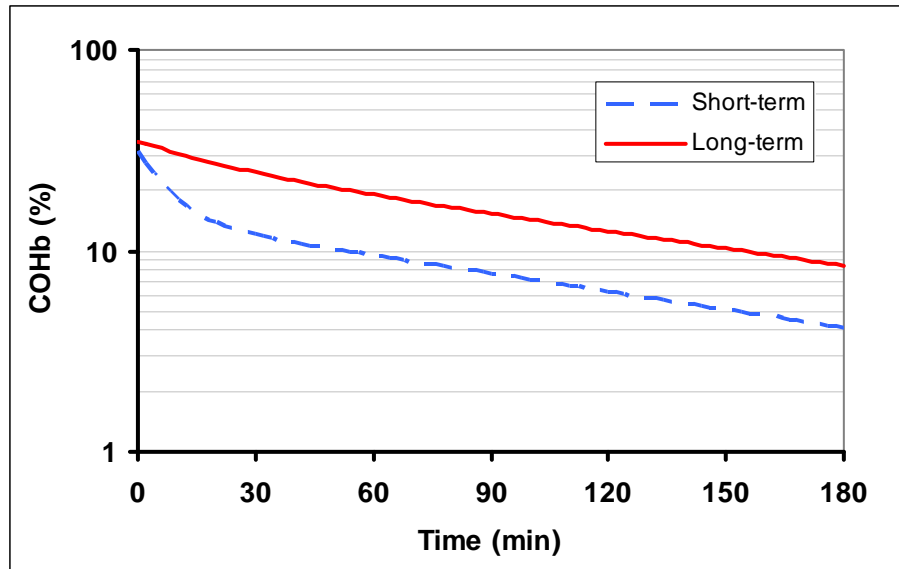
Adapted from Shimazu et al. (2000)

Figure 4-6.   **Changes in blood COHb after short-term and long-term exposure to CO, representing the biphasic nature of CO elimination. Note: y-axis is log-scale.**

4.4. Conditions Affecting Uptake and Elimination

4.4.1. Environment and Activity

1   Elevated CO exposure and COHb levels are dependent upon the changes in CO concentration in
2   the local environment. Pedestrians are exposed to high levels of CO for short time periods from vehicle
3   exhaust at busy intersections (see also Chapter 3.6). Higher exposure can also result from riding in an
4   automobile or stopping at busy intersections (Ott, 1994). Indoor exposure occurs from ETS and unvented
5   combustion appliances, such as natural gas cooking stoves, attached garages, and gas fireplaces, which
6   can accumulate to over 100 ppm (Dutton et al., 2001). Recreational exposure at levels exceeding 200 ppm
7   and peaks of 1,600 ppm could occur in indoor ice rinks using fossil fuel powered ice resurfacers and
8   coliseums housing malfunctioning equipment or poor ventilation (Levesque et al., 2000; Pelham et al.,
9   2002). Certain occupations provide instances and conditions for transient moderate-to-high CO levels,
10   including fire fighters and machinery operators. Such transient exposures have the ability to increase
11   COHb levels. For example, exposure for 5 minutes or less of a resting individual to 6,600 ppm CO will
12   result in up to 20% COHb (Benignus et al., 1994).
13   Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in
14   gas exchange. O_2 consumption can increase more than 10 fold during exercise. Similarly, ventilation,

1 membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase
2 proportional to work load. The majority of these changes facilitate CO uptake and transport, by increasing
3 gas exchange efficiency.
4   The COHb elimination rate decreases with physical activity (Joumard et al., 1981). Healthy
5 subjects exposed to CO and achieving COHb levels of approximately 4-5% observed a significant
6 detriment to exercise duration and maximal effort capability (measured by metabolic equivalent units)
7 (Adir et al., 1999). It is possible that CO lowers the anaerobic threshold, allowing earlier fatigue of the
8 skeletal muscles and decreased maximal effort capability.

4.4.2. Altitude

9   Increased altitude changes a number of factors that contribute to the uptake and elimination of CO.
10 The relationship between altitude and CO exposure has been discussed in depth in the 2000 AQCD and
11 other documents (U.S. EPA, 1978). In an effort to maintain proper O_2 transport and supply, physiological
12 changes occur as compensatory mechanisms to combat the decreased barometric pressure and resulting
13 altitude induced hyperbaric hypoxia (HH). HH, unlike CO hypoxia, causes humans to hyperventilate,
14 which reduces arterial blood CO_2 (hypocapnia) and increases alveolar partial pressure of O_2. Hypocapnia
15 will lead to difficulty of O_2 dissociation and decreased blood flow, thus reducing tissue O_2 supply. HH
16 increases blood pressure (BP) and cardiac output and leads to redistribution of blood from skin to organs
17 and from blood vessels to extravascular compartments. Generally these changes will favor increased CO
18 uptake and COHb formation, as well as CO elimination. In hypoxic conditions both CO and O_2 bind
19 reduced Hb through a competitive-parallel reaction (Chakraborty et al., 2004). Breathing CO (9 ppm) at
20 rest at altitude produced higher COHb compared to sea level (McGrath et al., 1993), whereas high altitude
21 exposure with exercise caused a decrease in COHb levels versus similar exposure at sea level (Horvath et
22 al., 1988). This decrease could be a shift in CO storage or suppression of COHb formation, or both.
23 Altitude also increases the baseline COHb levels by inducing endogenous CO production. Initial HH
24 increased lung HO-1 protein and activity, whereas chronic HH induced endogenous CO production in
25 nonpulmonary sites (see Section 4.5) (Carraway et al., 2000).
26   As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation,
27 polycythemia or increased red blood cell count, and increased tissue capillarity and Mb content in skeletal
28 muscle, which could also favor increased CO uptake. Most of the early adaptive changes gradually revert
29 to sea level values. However, differences in people raised at high altitude persist even after
30 reacclimatization to sea level (Hsia, 2002).

4.4.3. Physical Characteristics

1   Certain physical characteristics (e.g., age, sex, pregnancy) can alter the variables that influence the
2   uptake, distribution, and elimination of CO. Values of CO uptake and elimination change with age. Young
3   children eliminate COHb more rapidly than adults after CO exposure (Joumard et al., 1981; Klasner et al.,
4   1998). After infancy, the COHb half-life increases with age, nearly doubling between 2 and 70 years
5   (Joumard et al., 1981). The rate of this increase in CO elimination is very rapid in the growing years (2 to
6   16 years of age), but slows beyond adolescence. Alveolar volume and $D_L CO$ increase with increasing
7   body length of infants and toddlers (Castillo et al., 2006), suggesting a further degree of lung
8   development and faster CO uptake. After infancy, increasing age decreases $D_L CO$ and increases V_A/Q
9   mismatch, causing it to take longer to both load and eliminate CO from the blood (Neas and Schwartz,
10   1996).

11   COHb concentrations are generally lower in female subjects than in male subjects (Horvath et al.,
12   1988) and the COHb half-life may be longer in healthy men than in women of the same age, which may
13   be partially explained by differences in muscle mass or the slight correlation between COHb half-life and
14   increased height (Joumard et al., 1981). The rate of decline of $D_L CO$ with age is lower in middle-aged
15   women than in men; however, it evens out towards older age (Neas and Schwartz, 1996). Women also
16   tended to be more resistant to altitude hypoxia (Horvath et al., 1988).

17   Fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure, making it
18   difficult to estimate fetal COHb based on maternal levels. Human fetal Hb has a higher affinity for CO
19   than adult Hb (Di Cera et al., 1989). Maternal and fetal COHb concentrations have been modeled as a
20   function of time using a modified CFK equation (Hill et al., 1977). At steady-state conditions, the fetal
21   COHb is up to 10% higher than the maternal COHb levels, for example, exposure to 30 ppm CO results
22   in a maternal COHb of 5% and a fetal COHb of 5.5%. The fetal CO uptake lags behind the maternal for
23   the first few hours but later may overtake the maternal values. Similarly, during washout, the fetal COHb
24   levels are maintained for longer, with a half-life of around 7.5 hours versus the maternal half-life of
25   around 4 hours.

26   Ethnicity does alter physiological variables that determine CO uptake and kinetics. Lung volumes
27   are 10-15% less in both Asian and African-American populations when compared to Caucasians. This
28   causes a reduced alveolar surface area (20% less than estimated values) for gas exchange, leading to a
29   13% difference in diffusion capacity, $D_L CO$ (Pesola et al., 2004; Pesola et al., 2006). Certain factors such
30   as socioeconomic status (SES) were not controlled for in these studies. SES has been shown to affect
31   pulmonary function, including decreasing $D_L CO$ (Hegewald and Crapo, 2007).

4.4.4. Health Status

1   Health status can influence the toxicity involved with CO exposure by influencing the severity of
2   hypoxia resulting from CO exposure. Any condition that would alter the blood O_2 carrying capacity or
3   content will result in a greater risk from COHb induced hypoxia and decreased tissue O_2 delivery. The
4   severity of this effect depends upon the initial level of hypoxia.
5   Anemias are a group of diseases that result in insufficient blood O_2 or hypoxia due to Hb
6   deficiency through hemolysis, hemorrhage, or reduced hematopoiesis. Anemia may result from pathologic
7   conditions characterized by chronic inflammation such as malignant tumors or chronic infections
8   (Cavallin-Stahl et al., 1976a, b). The bodies of people with anemia compensate causing cardiac output to
9   increase as both heart rate and stroke volume increase. The endogenous production of CO, thus COHb, is
10   increased in patients with hemolytic anemia due to increased heme catabolism, causing an increased
11   baseline COHb concentration. One of the most prevalent anemias arises from a single-point mutation of
12   Hb, causing sickle cell diseases. The Hb affinity for O_2 and O_2 carrying capacity is reduced causing a shift
13   to the right in the O_2 dissociation curve. It is well documented that African-American populations have a
14   higher incidence of sickle cell anemia, which may be a risk factor for CO hypoxia.
15   Chronic obstructive pulmonary disease (COPD) is often accompanied by a number of changes in
16   gas exchange, including increased deadspace volume (V_D) and ventilation-perfusion ratio (V/Q)
17   inequality (Marthan et al., 1985), which could slow both CO uptake and elimination. Patients with
18   pulmonary sarcoidosis may have a decrease in lung volumes, a loss of D_LCO, and gas exchange
19   abnormalities during exercise, including decreased arterial oxygen pressure (P_aO_2) and increased alveolar-
20   arterial oxygen pressure difference (Lamberto et al., 2004).
21   Individuals with heart disease may be at a greater risk from CO exposure since they may already
22   have compromised O_2 delivery. Time to onset of angina was reduced after exposure to 100 ppm carbon
23   monoxide, compared to clean air (Kleinman et al., 1998). Hyperlipidemic patients may have decreased
24   CO diffusion capacity, a loss of V/Q gradient, and a decrease in P_aO_2 (Enzi et al., 1976).

4.5. Endogenous CO Production and Metabolism

25   Humans breathing air containing no environmental sources of CO will still have a low measurable
26   level of circulating COHb. This is due to endogenous CO production from heme protein catabolism
27   among other sources. In the natural degradation of RBC Hb, the porphyrin ring of heme is broken at the
28   methene bridge and catabolized in an O_2 dependent manner by HO complexed with NADPH-cytochrome
29   P450 reductase and biliverdin reductase to biliverdin, Fe, and CO. Biliverdin is then further broken down
30   into bilirubin, a powerful endogenous antioxidant. Two main HO isoforms exist, HO-1 and HO-2.

1   Expression of HO-1 is inducible, whereas HO-2 is constitutively expressed. The major site of heme

2   catabolism, thus the major organ of CO production is the liver, followed by the spleen, brain, and

3   erythropoietic system (Berk et al., 1976). These rates of CO formation may be due to higher levels of HO

4   activity in these tissues. The whole body production rate of CO is approximately 16.4 μmol/h (0.42 mL/h)

5   and produces between 400-500 μmol CO per day (Coburn et al., 1964; Coburn et al., 1966; Coburn,

6   1970b). The endogenous rate of CO formation has been shown to vary little between different tissues,

7   ranging from 0.029 nmol/mg protein/h in chorionic villi of term human placenta to 0.28 nmol/mg

8   protein/h in rat olfactory receptor neurons in culture and in rat liver perfusate (Marks et al., 2002),

9   however these estimations are questionable since CO is quickly scavenged in the cytosol of living cells.

10   CO is endogenously produced in the nose and paranasal sinus which may contribute to exhaled CO

11   concentrations (Andersson et al., 2000).

12   HO mediated metabolism functions as the rate-limiting enzyme step in heme degradation and

13   endogenous CO production (Wu and Wang, 2005). Three isoforms of HO exist, but HO-1 is the only

14   inducible form (Maines and Kappas, 1974; Maines et al., 1986; McCoubrey et al., 1997). Endogenous CO

15   production can be increased by the up-regulation of HO-1 expression and activity by inducers such as

16   oxidative stress, hypoxia, heavy metals, sodium arsenite, heme and heme derivatives, various cytokines,

17   and also exogenous CO (Wu and Wang, 2005). High levels of CO (2,500 ppm) have been shown to

18   increase HO-1 activity in the brain of rats, as well as liberate intracellular heme to further stimulate

19   endogenous CO production (Cronje et al., 2004).

20   Not all endogenous CO production is derived from Hb breakdown. Other hemoproteins, such as

21   Mb, cytochromes, peroxidases, and catalase, contribute 20-25% to the total amount of endogenous CO

22   (Berk et al., 1976). All of these sources result in a normal blood COHb concentration between 0.4 and

23   0.7% (Coburn et al., 1965). This baseline level of endogenous production can be altered by drugs or a

24   number of physiological conditions that alter RBC destruction, other hemoprotein breakdown, or bilirubin

25   production. Because of this sensitivity, ranges of endogenous COHb levels in the population are

26   uncertain. Nicotinic acid (Lundh et al., 1975), allyl-containing compounds (acetamids and barbiturates)

27   (Mercke et al., 1975b), diphenylhydantoin (Coburn, 1970b), progesterone (Delivoria-Papadopoulos et al.,

28   1974), and contraceptives (Mercke et al., 1975a) will increase CO production. Compounds such as carbon

29   disulfide and sulfur-containing chemicals (parathion and phenyltiourea) will increase CO by acting on

30   P450 system moieties (Landaw et al., 1970). The P450 system may also cause large increases in CO

31   produced from the metabolic degradation of dihalomethanes leading to very high (>10%) COHb levels

32   (Manno et al., 1992), which can be further enhanced by prior exposure to HCs or ethanol (Pankow et al.,

33   1991; Wirkner and Poelchen, 1996). HO can catalyze the release of CO from the auto-oxidation of

34   phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers

35   et al., 1994).

1   Any disturbance in RBC hemostasis by acceleration of destruction of hemoproteins will lead to

2   increased production of CO. Pathologic conditions such as anemias, hematomas, thalassemia, Gilbert's

3   syndrome with hemolysis, and other hematological diseases and illness will accelerate CO production

4   (Berk et al., 1974; Hampson, 2007; Meyer et al., 1998; Solanki et al., 1988). Patients with hemolytic

5   anemia exhibit COHb levels 2- to 3-times higher than healthy individuals and CO production rates 2- to

6   8-times higher (Coburn et al., 1966). Endogenous CO production rate varied from 0.70 to 3.44 mL/h in

7   anemic patients (Coburn et al., 1965). Women experience fluctuating COHb levels during pregnancy as

8   well as through the menstrual cycle when endogenous CO production doubles in the progesterone phase

9   (Delivoria-Papadopoulos et al., 1974; Mercke and Lundh, 1976).

10   Altitude has been shown to be positively associated with baseline COHb concentrations (McGrath,

11   1992; 1993). This increase in COHb with altitude induced hypoxia has also been associated with

12   increases in the mRNA, protein, and activity of HO-1 in rats and cells leading to enhanced endogenous

13   CO production (Carraway et al., 2002; Lee et al., 1997). Whether other variables such as an accelerated

14   metabolism or a greater pool of Hb, transient shifts in body stores, or a change in the elimination rate of

15   CO play a role has not been explored.

16   Endogenous CO is removed from the body mainly by expiration and oxidation. CO will diffuse

17   across the alveolar-capillary membrane and then is exhaled. This event has been used as a noninvasive

18   measurement of endogenous CO and CO body load (Stevenson et al., 1979). CO can also be oxidized to

19   CO_2 by cytochrome c oxidase in the mitochondria (Fenn, 1970; Young and Caughey, 1986). However, the

20   rates of CO metabolism are much slower than the rates of endogenous CO production, with the rate of

21   consumption representing only 10% of the rate of CO production in dogs (Luomanmaki and Coburn,

22   1969).

4.6. Summary and Conclusions

23   CO elicits various health effects by binding with and altering the function of a number of heme-

24   containing molecules, mainly Hb. The formation of COHb reduces the O_2-carrying capacity of blood and

25   impairs the release of O_2 from O_2Hb to the tissues. COHb formation has been modeled mainly by the

26   CFK equation, but more recent models have included Mb and extravascular storage compartments, as

27   well as other dynamics of CO physiology. These models have indicated that CO has a biphasic

28   elimination curve, due to initial washout from the blood followed by a slower flux from the tissues. The

29   flow of CO between the blood and alveolar air or tissues is controlled by diffusion down the CO

30   concentration gradient. The uptake of CO is governed not only by this CO pressure differential, but also

31   by physiological factors, such as minute ventilation and lung diffusing capacity, that can, in turn, be

32   affected by conditions such as exercise, age, and health. Susceptible populations, including health

1   compromised individuals and developing fetuses, are at a greater risk from COHb induced health effects

2   due to altered CO kinetics, compromised cardiopulmonary processes, and increased baseline hypoxia

3   levels. Altitude may also significantly affect the kinetics of COHb formation. Compensatory mechanisms,

4   such as increased cardiac output, combat the decrease in barometric pressure. Altitude also increases the

5   endogenous production of CO through upregulation of HO-1. CO is considered a second messenger and

6   is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1. Finally, CO is

7   removed from the body by expiration and oxidation to CO_2.

Chapter 5. Integrated Health Effects

5.1. Mode of Action of CO Toxicity

5.1.1. Introduction

1   The diverse effects of CO are dependent upon concentration and duration of exposure as well as on
2   the cell types and tissues involved. Responses to CO are not necessarily due to a single process and may
3   instead be mediated by a combination of effects including COHb-mediated hypoxic stress and
4   mechanisms unrelated to tissue hypoxia including free radical production and the initiation of cell
5   signaling. However, binding of CO to reduced iron in heme proteins with subsequent alteration of heme
6   protein function is the common mechanism underlying the biological responses to CO.

5.1.2. Hypoxic Mechanisms

7   As discussed in the 2000 CO AQCD, the most well-known pathophysiological effect of CO is
8   tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the O_2-
9   carrying capacity of blood, but it also impairs the release of O_2 from O_2Hb. Compensatory alterations in
10   hemodynamics, such as vasodilation and increased cardiac output, protect from tissue hypoxia. At
11   ambient CO concentrations, these compensatory changes are slight and likely tolerable in people with a
12   healthy cardiovascular system. However, people with cardiovascular detriments may be unable to endure
13   these small changes in hemodynamics which may lead to the presentation of health effects as described in
14   Sections 5.2.1 and 5.2.2.
15   The 2000 CO AQCD reported changes in vasodilation due to CO levels between 500-2000 ppm
16   (Kanten et al., 1983; MacMillan, 1975). Vasodilation can be dependent on or independent of perturbations
17   in O_2 supply (Koehler et al., 1982). For example, cerebral blood flow elevations that were independent of
18   O_2 availability were blocked by the inhibition of nitric oxide synthase (NOS) indicating a role for the free
19   radical species nitric oxide (NO$^\bullet$) in mediating vasodilation (Meilin et al., 1996).
20   Increased cardiac ouput was also discussed in the 2000 CO AQCD as a compensatory response to
21   CO-mediated tissue hypoxia. Findings of studies measuring hemodynamic alterations following CO
22   exposure were equivocal and sometimes contradictory (Penney, 1988). While most studies reported a
23   positive correlation between COHb and cardiac output at COHb levels above 20%, one study
24   demonstrated increased cardiac output in humans following acute exposure to 5% CO resulting in COHb
25   levels around 9% (Ayres et al., 1973). There was no increase in cardiac output following acute exposure

1   to 0.1% CO in this latter study. Increased heart rate and stroke volume (SV) were also observed in

2   response to CO exposure (Stewart et al., 1973b); however, some experiments found no change in SV in

3   humans with 18-20% COHb (Vogel and Gleser, 1972) or 12.5% COHb (Klausen et al., 1968). The 2000

4   CO AQCD reported that BP was generally unchanged in human CO exposure studies, while a number of

5   animal studies demonstrated CO-induced hypotension (Penney et al., 1988). No changes in forearm blood

6   flow, BP, or heart rate were reported in humans experiencing approximately 8% COHb (Hausberg and

7   Somers, 1997). However, high concentration animal exposures (3,000 to 10,000 ppm) showed diminished

8   organ blood flow (Brown and Piantadosi, 1992). In depth discussion of hemodynamic changes resulting

9   from CO exposure in recent human clinical studies can be found in Section 5.2.2.

10   Binding of CO to Mb, as discussed in the 2000 CO AQCD and in Section 4.3.2.3, can also impair

11   the delivery of O_2 to tissues. Mb has a high affinity for CO; however, physiological effects are seen only

12   after high dose exposures to CO, resulting in COMb concentrations far above baseline levels. High

13   energy phosphate production in cardiac myocytes was inhibited when COMb concentrations exceeded

14   40%, corresponding to an estimated COHb level between 20-40% (Wittenberg and Wittenberg, 1993).

15   Conversely, rat hearts perfused with 6% CO (60,000 ppm) exhibited no change in high energy phosphate

16   production, respiration rate, or contractile function (Chung et al., 2006; Glabe et al., 1998). These

17   conflicting studies employed CO levels that are not relevant for ambient exposure to CO.

5.1.3. Non-Hypoxic Mechanisms

18   Non-hypoxic mechanisms underlying the biological effects of CO were discussed in the 2000 CO

19   AQCD and are summarized below. Most of these mechanisms are related to CO's ability to bind heme-

20   containing proteins other than Hb and Mb (Raub and Benignus, 2002). Since then, additional experiments

21   have confirmed and extended these findings. While the majority of the older studies utilized

22   concentrations of CO far higher than ambient levels, many of the newer studies have employed more

23   environmentally relevant levels of CO.

5.1.3.1. Non-Hypoxic Mechanisms Reviewed in the 2000 CO AQCD

24   Inhibition of heme-containing proteins such as cytochrome *c* oxidase and cytochrome P450

25   oxidases may alter cellular function. CO interacts with the ferrous heme a_3 of the terminal enzyme of the

26   electron transport chain, cytochrome *c* oxidase (Petersen, 1977). Cytochrome *c* oxidase inhibition not

27   only interrupts cellular respiration and energy production, but can also enhance reactive oxygen species

28   (ROS) production. In vivo studies observed CO binding to cytochrome *c* oxidase under conditions where

29   COHb concentrations are above 50% (Brown and Piantadosi, 1992). It is unlikely that this could arise

30   under physiological conditions or under conditions relevant to ambient exposures.

1   Studies indicated that CO exposure produces a pro-oxidant cellular environment by a second

2   mechanism. CO exposure at concentrations of 10-20 ppm and above caused platelets of laboratory rats, as

3   well as cultured bovine pulmonary endothelial cells, to release $NO^\bullet$ (Thom and Ischiropoulos, 1997). An

4   increase in available $NO^\cdot$ was also seen in the lung and brain of CO-exposed rats (Ischiropoulos et al.,

5   1996; Thom et al., 1999b). $NO^\bullet$ combines with superoxide to form the highly active oxidant species,

6   peroxynitrite (Thom et al., 1997), which can lead to the activation and sequestration of leukocytes in brain

7   vessels (Thom et al., 2001b) and aorta, oxidation of plasma lipoproteins (Thom et al., 1999a), and the

8   formation of protein nitrotyrosine (Ischiropoulos et al., 1996; Thom et al., 1999a; Thom et al., 1999b).

9   The mechanism leading to $NO^\bullet$ release is likely the displacement of $NO^\cdot$ from nitrosyl bound Mb ($NO^\bullet$-

10   Mb) or Hb ($NO^\cdot$-Hb) by CO. The rate of this event is slow; however it occurs at environmentally relevant

11   concentrations of CO (Thom et al., 1997).

12   CO exposure also increases the production of other pro-oxidant species, including hydrogen

13   peroxide (H_2O_2) and hydroxyl radical ($OH^\cdot$). High level CO exposure (2,500 ppm) increases $OH^\bullet$ in rat

14   brain and this response is distinct from tissue hypoxia (Piantadosi et al., 1997). The mechanism for

15   enhanced H_2O_2 production is unclear. The release of H_2O_2 in the lung of CO-exposed rats was dependent

16   upon the production of $NO^\bullet$, as it was inhibited by the pretreatment with a NOS inhibitor (Thom et al.,

17   1999b). It is possible that peroxynitrite formed after CO exposure inhibited electron transport at

18   complexes I through III, or that cytochrome *c* oxidase interference led to mitochondrial dysfunction and

19   ROS production.

20   It has also been suggested that CO leads to vasorelaxation by three different mechanisms. First, CO

21   may inhibit the P450-dependent synthesis of vasoconstrictors (Wang, 1998). Vasodilation has been

22   demonstrated via this P450-mediated mechanism with high concentrations of CO (approximately

23   90,000 ppm) (Coceani et al., 1988). In the case of cytochrome P450 enzymes, tissue CO levels may have

24   to be abnormally increased to elicit a physiological response since the in vitro Warburg binding

25   coefficients, the ratio of CO to O_2 at which half the reactive sites are occupied by CO, for cytochrome

26   P450s range from 0.1-12 (Piantadosi, 2002). P450 inhibition may also reduce the hypoxia-induced

27   expression of mitogens such as erythropoietin (EPO), vascular endothelial growth factor (VEGF),

28   endothelin-1 (ET-1), and platelet derived growth factor (PDGF) which may decrease smooth muscle

29   proliferation in response to hypoxia (Wang, 1998). CO may also interfere with the metabolism of

30   barbiturates and other drugs; however, this is probably due to the hypoxic actions of CO rather than to

31   P450 inhibition (Roth and Rubin, 1976a, b).

32   Secondly, CO has been shown to play a physiological role in vasomotor control and in signal

33   transduction by activation of soluble guanylate cyclase (sGC), causing a conversion of GTP to cyclic

34   GMP (cGMP). CO interacts with sGC and forms an unstable complex with the heme core of the protein.

35   The resulting porphyrin IX intermediate triggers cGMP production (Ndisang et al., 2004). CO causes

36   vascular relaxation, independent of the endothelium, in human arterial rings (Achouh et al., 2008), rat tail

1 artery (Wang et al., 1997), and rat thoracic aorta (Lin and McGrath, 1988), but not cerebral vessels
2 (Andresen et al., 2006; Brian et al., 1994). Activation of sGC by CO has been linked to
3 neurotransmission, vasodilation, bronchodilation, inhibition of platelet aggregation, and inhibiton of
4 smooth muscle proliferation (Brune and Ullrich, 1987; Cardell et al., 1998; Morita et al., 1997; Verma et
5 al., 1993).
6   CO-mediated vasorelaxation can also be caused by activation of voltage-activated potassium (K^+)
7 channels or calcium (Ca^{2+})-activated K^+ channels, which leads to membrane hyperpolarization, voltage-
8 dependent Ca^{2+} channel closing, reduction of resting Ca^{2+} concentration, and then vascular tissue
9 relaxation (Farrugia et al., 1993; Wang et al., 1997). This effect may be linked to sGC activity; however it
10 has also been reported to occur independently (Dubuis et al., 2003; Naik and Walker, 2003).
11 Developmental stage and tissue type will determine whether K^+ channels or the sGC/cGMP pathway
12 plays more of a role in vasorelaxation (Ndisang et al., 2004).
13   Collectively, these older studies demonstrated that exposures to high concentrations of CO resulted
14 in altered functions of heme proteins other than Hb and Mb. Decreased cellular respiration and energy
15 production and increased pro-oxidant status following cytochrome c oxidase inhibition would likely
16 predispose towards cellular injury and death. The increase in free NO$^\bullet$ following its release from
17 sequestered stores could also contribute to the pro-oxidant status. Increased ROS and reactive nitrogen
18 species are known to promote cell signaling events leading to inflammation and endothelial dysfunction.
19 An inappropriate increase in vasorelaxation due to inhibition of vasoconstrictor production or to
20 activation of vasodilatory pathways (sGC and ion channels) could potentially limit compensatory
21 alterations in hemodynamics. Alternatively, CO-binding to sGC could result in decreased vasorelaxation
22 by interfering with the binding of NO$^\bullet$ to sGC. NO$^\bullet$ can also activate sGC, and with a 30-fold greater
23 affinity than CO is one-thousand fold more potent with respect to vasodilation and sGC activation (Stone
24 and Marletta, 1994). CO could further contribute to endothelial dysfunction by this mechanism. Although
25 the 2000 CO AQCD made no definitive links between these non-hypoxic mechanisms of CO and
26 CO-mediated health effects, it did establish the potential for CO to interfere with basic cellular and
27 molecular processes which could lead to dysfunction and/or disease.

5.1.3.2. Recent Studies of Non-Hypoxic Mechanisms

28   Since the 2000 CO AQCD, new studies have provided additional evidence for non-hypoxic
29 mechanisms of CO which involve the binding of CO to reduced iron in heme proteins. These
30 mechanisms, which may be inter-related, are described below and include:

1   ▪ Alteration in NO• signaling

2   ▪ Inhibition of cytochrome *c* oxidase

3   ▪ Heme loss from protein

4   ▪ Disruption of iron homeostasis

5   ▪ Alteration in cellular redox status

6   This assessment evaluates these non-hypoxic mechanisms in terms of their potential to contribute

7   to health effects associated with environmentally-relevant CO exposures. As discussed above, CO at high

8   concentrations may promote oxidative stress, cell injury and death, inflammation and endothelial

9   dysfunction. Whether lower CO concentrations trigger these same processes is of key interest since these

10   can potentially contribute to adverse health effects.

11   In addition, a large number of studies published since the 2000 CO AQCD has focused on the role

12   of COs as an endogenous signaling molecule and the potential therapeutic effects of exogenous CO

13   administered at high concentrations. This assessment addresses these topics only briefly, as they pertain to

14   the evaluation of health effects associated with environmentally-relevant CO exposures.

Alteration in NO• Signaling

15   Work by Thorup et al. (1999) demonstrated altered NO• signaling in isolated rat renal resistance

16   arteries. In one set of experiments, rapid release of NO• was observed in response to a supra-physiologic

17   dose of CO (100 nM). These findings are similar to those of Thom and colleagues (Ischiropoulos et al.,

18   1996; Thom et al., 1994; Thom and Ischiropoulos, 1997; Thom et al., 1997; Thom et al., 1999a; Thom et

19   al., 1999b; Thom et al., 2000; Thom et al., 2006) who demonstrated NO• release, presumably from

20   sequestered stores, in platelets, endothelial cells, aorta and lung in response to CO (see above).

21   Furthermore in a second set of experiments, Thorup et al. (1999) demonstrated inhibition of NOS in

22   isolated rat renal resistance arteries. Here rapid NOS-dependent release of NO• following carbachol

23   stimulation was blocked by pretreatment with 100 nM NO•. Both sets of studies illustrate the potential of

24   CO to alter processes dependent on endogenous NO•. This could be critical in the case of cGMP-

25   mediated vasodilation since, as discussed above, NO• activates sGC to a greater extent than CO. Thus in

26   the presence of excess CO, NO•-dependent vasodilation may be significantly less.

Inhibition of Cytochrome *c* Oxidase

27   High concentrations of CO are known to inhibit cytochrome *c* oxidase, the terminal enzyme in the

28   mitochondrial electron transport chain, resulting in inhibition of cellular respiration and the formation of

29   superoxide from mitochondrial substrates. Several recent studies demonstrated CO-mediated decreases in

30   cytochrome *c* oxidase activity in model systems ranging from isolated mitochondria to whole animals. In

1   a study by Alonso et al. (2003), exposure of isolated mitochondria from human skeletal muscle to 50-
2   500 ppm CO for 5 min decreased cytochrome c oxidase activity. Similarly, exposure of cultured
3   macrophages to 250 ppm CO for 1 h inhibited cytochrome c oxidase (Zuckerbraun et al., 2007). In this
4   study, increased ROS were observed following exposure to 250 ppm, as well as to CO concentrations as
5   low as 50 ppm, for 1 h. Animal studies demonstrated that exposure of rats to 250 ppm CO for 90 min
6   inhibited cytochrome c oxidase activity in myocardial fibers (Favory et al., 2006a) and exposure of mice
7   to 1,000 ppm CO for 3 h decreased cytochrome c oxidase activity in heart mitochondria (Iheagwara et al.,
8   2007). COHb levels were reported to be 61% in the latter study.

Heme Content Loss from Proteins

9   In addition to decreasing the activity of cyctochrome c oxidase, exposure of mice to 1,000 ppm CO
10 for 3 h resulted in decreased protein levels and heme content of cytochrome c oxidase (Iheagwara et al.,
11 2007). CO-mediated heme release was also seen in a study by Cronje et al. (2004), and was followed by
12 increased endogenous CO production through the activation of HO-2 and the induction of HO-1. Loss of
13 heme from proteins leads to loss of protein function and often to protein degradation.

Disruption of Iron Homeostasis

14 Exposure of rats to 50 ppm CO for 24 h increased levels of iron and ferritin in the bronchoalveolar
15 lavage fluid (BALF), decreased lung non-heme iron and increased liver non-heme iron (Ghio et al.,
16 2008). Furthermore in this same study, exposure of respiratory epithelial cells to 10-100 ppm CO for 24 h
17 caused a dose-dependent decrease in cellular non-heme iron and ferritin. Heme loss observed in other
18 studies (Cronje et al., 2004; Iheagwara et al., 2007) might be expected to result in disruption of iron
19 homeostasis. Iron homeostasis is critical for the sequestration of free iron and the prevention of iron-
20 mediated redox cycling which can lead to ROS generation and lipid peroxidation.

Alteration in Cellular Redox Status

21 Recent studies demonstrated that exposure to low, moderate and high levels of CO increased
22 cellular oxidant stress in cultured cells (Kim et al., 2008; Zuckerbraun et al., 2007). A dose-dependent
23 increase in dichlorofluoroscein (DCF) fluorescence (an indicator of ROS) occurred following 1-h
24 exposure to 50-500 ppm CO in macrophages and following 1-h exposure to 250 ppm CO in hepatocytes.
25 NOS inhibition had no effect on the increase in DCF fluorescence in CO-treated macrophages indicating
26 that the effects were not due to an interaction of CO and NO$^{\bullet}$ (Zuckerbraun et al., 2007). Mitochondria
27 were identified as the source of the increased ROS since mitochondria-impaired cells (rho zero cells and
28 treatment with antimycin A) did not respond to CO with an increase in DCF fluorescence. Furthermore,
29 1-h exposure to 250 ppm CO inhibited mitochondrial cytochrome c oxidase enzymatic activity in
30 macrophages (Zuckerbraun et al., 2007). Recently, inhibition of cytochrome c oxidase was demonstrated

1 in HEK-293 cells transfected with HO-1 and in macrophages with induced HO-1, and this effect was

2 attributed to endogenously produced CO (D'Amico et al., 2006). However inhibition of cytochrome *c*

3 oxidase at CO concentrations below 250 ppm has not been definitively demonstrated. In hepatocytes,

4 exposure to 250 ppm CO for 1 h resulted in Akt phosphorylation and nuclear translocation of nuclear

5 factor kappa B (NF-κB), effects which were blocked by antioxidants (Kim et al., 2008). Significant

6 increases in apoptosis were also observed in this model. Thus, CO appeared to uncouple mitochondrial

7 respiration leading to ROS-induced programmed cell death.

8 Further evidence for cellular redox stress is provided by studies in which glutathione stores were

9 altered following CO exposure in vitro (Kim et al., 2008; Patel et al., 2003). In addition, mitochondrial

10 redox stress was observed in livers of rats exposed to 50 ppm CO (Piantadosi et al., 2006). Furthermore,

11 an adaptive increase in intracellular antioxidant defenses (i.e., superoxide dismutase) was observed in

12 endothelial cells exposed to 10 ppm CO for 40 min (Thom et al., 2000) and mitochondrial biogenesis was

13 observed in hearts of mice exposed to 50 and 250 ppm CO for 1 h (Suliman et al., 2007).

14 Several mechanisms could contribute to the cellular redox stress elicited by CO exposure. As

15 discussed above, inhibition of cytochrome *c* oxidase results in the formation of superoxide from

16 mitochondrial substrates. However, interactions of CO with heme proteins can lead to the release of heme

17 and free iron which could also lead to the generation of ROS. As mentioned above, increased ROS

18 generation has been linked to cellular injury and death, inflammation, and endothelial dysfunction.

19 Two of the above-mentioned studies demonstrated that CO-mediated mechanisms were unrelated

20 to hypoxia by showing that hypoxic conditions failed to mimic the results obtained with CO. Hence the

21 mitochondrial redox stress and mitochondrial pore transition observed in livers from rats exposed to CO

22 (Piantadosi et al., 2006) and the cardiac mitochondrial biogenesis observed in mice exposed to CO

23 (Suliman et al., 2007) could be attributed specifically to non-hypoxic mechanisms of CO.

24 Recent studies also demonstrated non-hypoxic mechanisms of CO which do not directly involve

25 heme protein interactions. These mechanisms are described below and include:

26 ▪ Alteration in ion channel activity

27 ▪ Modulation of protein kinase pathways

Alteration in Ion Channel Activity

28 Work by Dubuis et al. (2002) demonstrated increased current through Ca^{2+}-activated K^+ channels in

29 smooth muscle cells from pulmonary arteries of rats exposed to 530 ppm CO for 3 weeks. These findings

30 provide further evidence for non cGMP-dependent vasodilatory actions of CO.

Modulation of Protein Kinase Pathways

1   Endogenously produced CO is a gaseous second messenger molecule in the cell. Work from
2   numerous laboratories has demonstrated the potential for CO to be used as a therapeutic gas with
3   numerous possible clinical applications, since it can produce anti-inflammatory, anti-apoptotic, and anti-
4   proliferative effects (Ryter et al., 2006). These studies generally involved pretreatment with CO followed
5   by exposure to another agent 18-24 h later. There is extensive literature on this topic as reviewed by Ryter
6   et al. (2006) and others. A number of these processes are mediated through cGMP while others involve
7   redox-sensitive kinase pathways, possibly secondary to CO-dependent generation of ROS. For example,
8   250 ppm CO inhibited growth of airway smooth muscle cells by attenuating the activation of the
9   extracellular signal-regulated kinase 1/2 (ERK 1/2) pathway, independent of sGC and other MAP kinases
10   (Song et al., 2002). A second example is provided by the study of Kim et al. (2005) where 250 ppm CO
11   inhibited PDGF- induced smooth muscle cell proliferation by upregulating $p21^{Waf1/Cip1}$ and caveolin-1, and
12   down-regulating cyclin A expression. These events were dependent upon cGMP and the p38 MAPK
13   pathway (Kim et al., 2005). Thirdly, rat endothelial cells exposed to 15 ppm CO escaped anoxia-
14   reoxygenation mediated apoptosis via modulation of the signaling pathways involving phosphoinositide
15   3-kinase (PI3K), Akt, p38 MAP kinase, Signal Transducers and Activators of Transcription (STAT-1) and
16   STAT-3 (Zhang et al., 2005). In a fourth study, Akt was found to be responsible for the CO-induced
17   activation of NF-κB, protecting against hepatocyte cell death (Kim et al., 2008). While research focusing
18   on therapeutic applications of CO generally involves high level, short-term exposure to CO (250-
19   1,000 ppm for up to 24 h), some studies found effects below 20 ppm (Zhang et al., 2005). Few if any
20   studies on the therapeutic effects of CO have explored the dose-response relationship between CO and
21   pathway activation/deactivation, so it remains unclear how these effects may be related to
22   environmentally-relevant exposures.

Concentration-Response Relationships

23   In many cases the concentrations of exogenous CO required for these non-hypoxic mechanisms is
24   much higher than what would be expected to result from exposures at ambient levels (Alonso et al., 2003;
25   Favory et al., 2006b; Iheagwara et al., 2007; Thorup et al., 1999). However in some studies the effects are
26   mimicked by upregulation of HO-1 which would result in increased local production of CO as well as of
27   iron and biliverdin (D'Amico et al., 2006; Imai et al., 2001; Thorup et al., 1999). For example, HO-1
28   overexpression attenuated carbachol-mediated NO• release and NO•-mediated vasodilation, similar to the
29   effects of exogenous CO in these same models (Imai et al., 2001; Thorup et al., 1999). In the study by
30   D'Amico et al. (2006), overexpression of HO-1 in cells inhibited cellular respiration by 12% and
31   decreased cytochrome c oxdase activity by 23%. It is not clear how comparable these conditions

1 involving increased intracellular concentrations of endogenous CO are to increased intracellular

2 concentrations of CO resulting from ambient CO exposures.

3   There is a growing appreciation that non-hypoxic mechanisms may contribute to the effects

4 associated with CO poisoning (Ischiropoulos et al., 1996; Thom et al., 1994; Weaver et al., 2007). On the

5 other hand, recent studies suggest that exogenous CO at low concentrations may have beneficial anti-

6 inflammatory, anti-proliferative and cytoprotective effects under certain circumstances (Ryter et al.,

7 2006). Since the focus of this assessment is on mechanisms which are relevant to ambient exposures it is

8 important to understand which mechanisms may occur at "low" (50 ppm and less) and "moderate"

9 (50-500 ppm CO) concentrations of CO. Hence, both recent animal studies and relevant older ones which

10 add to the understanding of mechanisms in this range of CO concentrations are briefly summarized in

11 Table 5-1. It should be noted that most of the above-mentioned non-hypoxic mechanisms are

12 demonstrated at CO concentrations of 50 ppm and less.

Table 5-1.   **Responses to low and moderate CO exposures.**

Reference	Model System	CO Exposure	Response	Notes
IN VITRO				
Alonso et al. (2003)	Human muscle mitochondria	50, 100, 500 ppm 5 min	Decreased cytochrome c oxidase activity	
Thom and Ischiropoulos (1997)	Rat platelets	10 ppm	Increased free NO$^\bullet$	
Thom et al. (1997)	Bovine pulmonary artery endothelial cells	20 ppm 30-60 min	Increased free NO$^\bullet$ and peroxynitrite	Reported to correspond to 7% COHb
Thom et al. (2000)	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)	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)	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)	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)	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)	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

Reference	Model System	CO Exposure	Response	Notes
Ghio et al. (2008)	Human bronchial epithelial cells	10-100 ppm 24 h	Dose-dependent decrease in cellular non-heme iron (effect at 10 ppm was signficant, 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 experiment in same paper

IN VIVO

Reference	Model System	CO Exposure	Response	Notes
Ghio et al. (2008)	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	
Thom et al., (1999b)	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., (1999a)	Rats	100 ppm 1 h 50 ppm 1 h	Elevated free NO$^\bullet$ 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)	Rats	200 ppm 72 weeks	No changes in lung morphology No pulmonary hypertension No atherosclerotic lesions in systemic vessels Ventricular hypertrophy	
Loennechen et al. (1999)	Rats	100 and 200 ppm 1-2 weeks	Increased ET-1 mRNA in the heart ventricles, increased right and left ventricular weight	12 and 23% COHb
Favory et al. (2006b)	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)	Rats	50 ppm CO or HH for 1, 3, or 7 days	Liver mitochondrial oxidative and nitrosative stress, altered mitochondrial permeability pore transition sensitivity	CO effects not mimicked by HH
Suliman et al. (2007)	Mice	50 and 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)	Rats Model of MI	35 ppm 1 h	Decreased delayed ventricular beat frequency	Altered arrhythmogenesis
Wellenius et al. (2006a)	Rats Model of MI	35 ppm 1 h	Decreased supraventricular ectopic beats	Altered arrhythmogenesis
Carraway et al. (2002)	Rats Model of hypoxic pulmonary vascular remodeling	Hypobaric hypoxia ± 50 ppm CO 3 weeks	CO promoted remodeling and increased pulmonary vascular resistance	
Gautier et al. (2007)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	3 weeks of HH 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)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	50 ppm 10 wk	CO increased cardiac dilation and decreased left ventricular function	

Reference	Model System	CO Exposure	Response	Notes
Melin et al. (2002)	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 Non-Hypoxic Mechamisms

1   A key issue in understanding the biological effects of environmentally-relevant exposures to CO is

2   whether the resulting partial pressures of CO in cells and tissues can initiate cell signaling or perturb

3   signaling which normally is mediated by endogenously generated CO.

4   Several aspects need to be considered. One is that, for most cells and tissues, Hb acts as a buffer to

5   limit the availability of free CO. At the same time, COHb delivers CO to cells and tissues. CO

6   dissociation from Hb occurs as a function of CO diffusion down a concentration gradient. Hence, greater

7   release of CO from COHb will occur under conditions of low cell/tissue CO concentration.

8   A second consideration is the role played by O_2 in competing with CO for binding to intracellular

9   heme protein targets. In general, heme proteins (e.g., cytochrome *c* oxidase) are more sensitive to CO

10   when O_2 is limited. Hence hypoxic conditions would be expected to enhance the effects of CO. This

11   concept is demonstrated in the study by D'Amico et al. (2006).

12   A third consideration is whether certain cell types serve as primary targets for the effects of CO.

13   Besides the RBC, the first cells encountering CO which dissociates from Hb will be the endothelial cells

14   lining blood vessels. White blood cells in the circulation may also be first-line targets of Hb-dissociated

15   CO. An exception to this situation is in the lungs where epithelial and inflammatory cells found in

16   airways and alveoli are exposed to free CO prior to CO binding to Hb. These lung cells may also serve as

17   unique targets for CO. Processes such as endothelial dysfunction, inflammatory cell activation and

18   respiratory epithelial injury may ensue as a result of preferential targeting of these cell types.

19   Fourth, it should be considered that adaptation to chronic exogenous CO exposure might occur and

20   that intermittent exogenous CO exposure might have unexpected effects.

21   Since there is potential for exogenous CO to affect endogenous pools of CO, it is important to

22   know the concentrations of CO in cells and tissues before and after exogenous exposures. Table 5-2

23   summarizes findings from 4 recent studies relevant to this issue. It should be noted that exposure to

24   50 ppm CO resulted in a 3-5 fold increased in tissue CO concentration.

Table 5-2.   Tissue concentration of CO following inhalation exposure.

Reference	CO Exposure	Tissue CO Concentrations	COHb	Notes
Cronje, et al. (2004)	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)
Vreman, et al. (2005)	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)	Rats 50 ppm 1-7 days	Liver: 30-40 pmol/mg Control liver 10 pmol/mg	4-5% Control 1%	CO concentration plateaued after 1 day
Suliman et al. (2007)	Mice 50, 250 and 1250 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)

1   Furthermore, endogenous CO production is increased during inflammation, hypoxia, increased

2 heme availability and other conditions where HO-1 or HO-2 activity is increased. A few studies reported

3 increased COHb levels and/or cell and tissue concentrations of CO resulting from enhanced endogenous

4 CO production. Table 5-3 summarizes these findings.

Table 5-3.   Tissue concentration of CO following increased endogenous production.

Reference	Exposure	Tissue CO	COHb	Notes
Carraway,et al. (2000)	Rats Hypobaric Hypoxia for 21 days		1.5-2.8% Control 0.5%	COHb highest after days 1 and 21 at 3-4 fold higher than controls
Piantadosi et al. (2006)	Rats Hypobaric Hypoxia 1-7 days	Liver: 5-12 pmol/mg Control liver 10 pmol/mg	1-1.25% Control 1%	CO concentration plateaued after 1 day
Vreman et al. (2005)	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%

1   It should be noted that increased cellular and tissue concentrations of biliverdin and iron

2 accompany the increased endogenous production of CO by HO-1 and HO-2. Biliverdin and iron have

3 known biological effects, with biliverdin exhibiting antioxidant properties and iron exhibiting pro-oxidant

4 properties (Piantadosi, 2008), which could impact interpretation of results from studies in which HO-1

5 and HO-2 activities are increased. Hence the situations of increased endogenous CO production and that

6 of exogenous CO exposure are not equivalent. Nonetheless, additional measurements of CO levels in cells

7 and tissues following increased endogenous production and following inhalation of exogenous CO is

8 essential for a better understanding of the relationship between the CO tissue dose and the response.

9   In summary, CO is a ubiquitous cell signaling molecule and the physiological functions of HO-

10 derived CO are numerous. The endogenous generation and release of CO from HO-1 and HO-2 is tightly

11 controlled, as is any homeostatic process. Thus, exogenously-applied CO has the capacity to disrupt

12 myriad heme-based signaling pathways due to its nonspecific nature. Only a limited amount of

13 information is available regarding the impact of exogenous CO on tissue and cellular levels of CO.

14 However recent animal studies demonstrated increased tissue CO levels and biological responses

15 following exposure to 50 ppm CO. Whether or not environmentally relevant exposures to CO can affect

16 endogenous CO signaling pathways and lead to adverse health effects is an open question for which there

17 are no definitive answers at this time.

5.2. Cardiovascular Effects

18   This section characterizes the evidence from epidemiologic, controlled human exposure and animal

19 toxicological studies on the cardiovascular effects of CO. While epidemiologic studies evaluated the

20 effects of ambient exposures, experimental studies employed higher than ambient concentrations of CO

21 but not levels of exposure associated with poisoning.

5.2.1. Epidemiologic Studies

22   The 2000 CO AQCD concluded that epidemiologic studies provided evidence that short-term

23 variations in ambient CO concentrations were associated with daily hospital admissions for heart disease.

24 The following section reviews the literature since the 2000 CO AQCD, including new studies on

25 physiological cardiac endpoints and biomarkers and additional studies of daily hospital admissions for

26 heart disease that support the evidence in the 2000 CO AQCD.

5.2.1.1. Epidemiologic Studies with Short-Term Exposure

Heart Rate and Heart Rate Variability

1   Heart rate variability (HRV) refers to the beat-to-beat alterations in the heart and is generally
2   determined by analyses of time and frequency domains measured by electrocardiograms (ECG). The time
3   domains often analyzed are (a) normal-to-normal (NN or RR) time interval between each QRS complex,
4   (b) standard deviation of the normal-to-normal interval (SDNN), and (c) mean squared differences of
5   successive difference normal-beat to normal-beat intervals (rMSSD), shorter time domain variables
6   results in lower HRV. The frequency domains often analyzed are a) the ratio of low energy frequency (LF)
7   to high energy frequency (HF) and b) the proportion of interval differences of successive normal-beat
8   intervals greater than 50 ms (PNN_{50}), reflecting autonomic balance. Decreased HRV is associated with a
9   variety of adverse cardiac outcomes such as arrhythmia, myocardial infarction (MI), and heart failure (De
10   Jong and Randall, 2005; Deedwania et al., 2005; Huikuri et al., 1999; Rajendra Acharya et al., 2006).
11   Two studies investigated the association between ambient air pollution, including CO, and HRV in
12   Boston, MA and reported inconsistent results. The earlier of these studies recruited twenty-one 53-to
13   87-year old active residents and performed up to 12 ECG assessments on each subject over a period of 4
14   months (during summer 1997). Particles (PM_{10}, $PM_{2.5}$) and several gaseous pollutants (O_3, NO_2, and SO_2)
15   were monitored at fixed sites (up to 4.8 miles from the study site) while CO was monitored 0.25 miles
16   from each participants' residence. Lag periods for the preceding 1-h, 4-h, and 24-h before each subject's
17   HRV assessment were analyzed and results showed that only $PM_{2.5}$ and O_3 were associated with HRV
18   parameters (Gold et al., 2000).
19   A similar study by the same group of researchers two years later involved 28 older subjects (aged
20   61-89) who were living at or near an apartment complex located on the same street as the Harvard School
21   of Public Health. The subjects were seen once a week for up to 12 weeks and HRV parameters (SDNN,
22   r-MSSD, PNN_{50}, LF/HF ratio) were measured for 30 minutes each session. Data for $PM_{2.5}$, black carbon
23   (BC), and CO were recorded at the Harvard School of Public Health (<1 km from the residence) while
24   data for NO_2, O_3, and SO_2 were collected from government regulatory monitoring sites. There were
25   moderate correlations between CO and $PM_{2.5}$ (r = 0.61) and NO_2 (r = 0.55), but not with SO_2 (r = 0.18) or
26   O_3 (r = 0.21). Similarly $PM_{2.5}$ was associated with HRV, whereas in contrast to the previous study, CO
27   was associated[1] with a negative change in SDNN (% change: -13 [95% CI: -24.06 to -1.88]), r-MSSD
28   (% change: -31.88 [95% CI: -38 to -7.5]), and PNN_{50} (% change: -46.25 [95% CI -103.95 to -9.38] per
29   0.5 ppm increase in 24-h avg CO concentration) (Schwartz et al., 2005).

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[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).

1   A later Boston, MA study examined HRV parameters (SDNN, LF, HF, LF/HF ratio) among 603

2   persons from the Normative Aging Study, a longitudinal study that originally recruited 2,280 men in the

3   greater Boston area during 1963. The cohort members were examined (November 2000 to October 2003)

4   and the ECG data were linked to air pollution data for $PM_{2.5}$, particle number concentration, BC, O_3, NO_2,

5   SO_2, and CO. Lagged pollutant effects for a 4-h, 24-h, and 48-h moving avg were used. Since previous

6   studies established variable CO results, the main pollutant effects were with $PM_{2.5}$ and O_3 while CO was

7   not associated with HRV (Park et al., 2005b).

8   A study in Mexico City selected 30 subjects from the outpatient clinic at the National Institute of

9   Cardiology and followed them for ~10 hours (starting at 0900 hrs) (Riojas-Rodriguez et al., 2006). Each

10   subject was connected to a Holter ECG monitor (e.g., a portable ECG monitor) and also given personal

11   $PM_{2.5}$ and CO monitors. The subjects went about their usual daily activities and the personal $PM_{2.5}$ and

12   CO data were linked to various ECG parameters (heart rate [HR], R-R, LF, HF) at various lags. In

13   copollutant models ($PM_{2.5}$ and CO) personal CO exposure for the same 5-min period was significantly

14   associated with a decrease in LF and very low energy frequency (VLF) parameters with coefficients equal

15   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

16   increase in 1-h CO concentration.

17   In Mexico City, 34 residents from a nursing home underwent HRV analysis every other day for 3

18   months (Holguin et al., 2003). Exposure assessment for ambient $PM_{2.5}$ was based on data recorded at a

19   monitor on the roof of the nursing home while exposures to ambient O_3, NO_2, SO_2, and CO were derived

20   from data recorded at a fixed site 3 km from the nursing home. Exposures for the same day and 1-day lags

21   were analyzed and only O_3 and $PM_{2.5}$ were positively associated with HRV.

22   Wheeler et al. (2006) examined 18 individuals with COPD and 12 individuals with recent MI

23   living in Atlanta, GA. Morning ECG readings were collected by a Holter system by a field technician in

24   the subjects' homes. Ambient air pollution exposures for $PM_{2.5}$, O_3, NO_2, SO_2 and CO were derived from

25   data recorded at fixed sites throughout metropolitan Atlanta. Three exposure periods were analyzed: the

26   hour of the ECG reading, 4-h mean and 24-h mean before the reading. While positive effects were

27   reported for NO_2 and $PM_{2.5}$, no quantitative results were reported for CO.

28   After reviewing 2,000 patient charts, Dales (2004) recruited 36 subjects with CAD from the

29   Toronto Western Hospital's noninvasive cardiac diagnostic unit. HR and HRV (SDNN, N-N, HF, LF,

30   HF/LH ratio) were assessed 1 day each week for up to 10 weeks by a Holter monitoring system. Personal

31   air sampling for $PM_{2.5}$ and CO was carried out for the same 24-h period whereby subjects went about

32   their usual daily activities for that period. Stratified results showed that among those not on beta-receptor-

33   blockers, personal CO exposure was positively associated with SDNN (p = 0.02). However, in the group

34   taking beta blockers there was a negative association (p = 0.06). Personal exposure to $PM_{2.5}$ was not

35   associated with HRV.

1   HR was examined among a sub-sample of the Monitoring of Trends and Determinants in
2   Cardiovascular Disease (MONICA) study (n = 2,681) in Augsburg, Germany by Peters and colleagues
3   (1999a). Total suspended particles (TSP), SO_2, and CO data were collected from a single monitoring
4   station located in the center of the city and linked to each subject to estimate exposures on the same day
5   and 5 days prior. A 0.5 ppm change in 24-h CO concentration was associated with an increase in HR of
6   approximately 1 beat per minute, whereas CO based on a 5-day exposure had no effect on HR.
7   Liao et al (2004) investigated men and women aged 45-64 years from the Atherosclerosis Risk in
8   Communities (ARIC) study (Washington County, MD; Forsyth County, NC; and selected suburbs of
9   Minneapolis, MN). The sample sizes were 4,899, 5,431, 6,232, 4,390 and 6,784 for analyses involving
10   PM_{10}, O_3, CO, NO_2, and SO_2 respectively. County level exposure estimates for 24 h CO were calculated
11   for 1, 2, and 3 days prior to clinical examination. A 0.5 ppm increase in 24-h CO concentration (at lag 1)
12   was associated with an increase in HR (beats/minute) (β = 0.357, p <0.05). CO was not significantly
13   associated with changes in SDNN.
14   The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study
15   was carried out in three European cities: Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki,
16   Finland, whereby a panel of subjects with CAD was followed for 6 months with biweekly clinical visits,
17   which included an ECG reading to assess HRV (Timonen et al., 2006). The time domain measures of
18   HRV (SDNN and rMSSD) were analyzed along with frequency domain measures, which included power
19   spectrum densities for LF and HF. Exposures to ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, CO) were
20   derived from data recorded at fixed monitoring site networks within each city. Correlation coefficients for
21   NO_2 and CO ranged from 0.32 to 0.86 in the three cities. CO was moderately correlated with PM_{10} in
22   Helsinki (r = 0.40) and with $PM_{2.5}$ in Amsterdam (r = 0.58) and more highly correlelated with PM_{10} in
23   Erfurt (r = 0.77). Various lag periods were examined including lag 0 (24 h prior to the clinical visit)
24   through a 0-2-day avg lag and a 0-4-day avg lag. In total there were 1,266 ECG recordings used in the
25   final analyses. In the pooled analyses (e.g., across cities) a 0.5 ppm increase in 24-h CO concentration
26   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
27   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],
28   respectively). However, the same study reported no effect for CO on BP and HR (Ibald-Mulli et al.,
29   2004).
30   A small panel study in Kuopio, Finland, which was designed as the pilot study for the ULTRA
31   study examined simultaneous ambulatory ECG and personally monitored CO readings among 6 male
32   patients with CAD (Tarkiainen et al., 2003). The patients were asked to follow their usual daily activities,
33   but data were recorded only three times with 1-week intervals. The CO exposures were divided into low
34   ($\leq$ 2.7 ppm) and high (>2.7 ppm) and during the high CO exposure r-MSSD increased on average by 2.4
35   ms. However, there was no effect on RR or SDNN.

1   A study in Taiwan recruited 83 patients (aged 40-75) from the National Taiwan University

2 Hospital, Taipei and conducted ambulatory ECG readings using a Holter system (Chan et al., 2005).

3 Ambient air pollution exposures for PM_{10}, NO_2, SO_2, and CO were derived from 12 fixed site monitoring

4 stations across Taipei. Lag periods of 1 h to 8 h prior to the ECG reading were analyzed and only NO_2

5 was associated with HRV parameters (SDNN and LF). CO was not associated with HRV.

6   The ST-segment of an ECG represents the period of slow repolarization of the ventricles and

7 ST-segment depression can be associated with adverse cardiac outcomes. Gold et al. (2005) recruited a

8 panel of 28 older adults living at or near an apartment complex located within 1 km of a monitoring site in

9 Boston, MA. Each subject underwent weekly ECGs for 12 weeks in summer 1999 with the main outcome

10 of interest being the ST-segment. Air pollution data in the form of $PM_{2.5}$, black carbon (BC), and CO were

11 collected from a central site within 0.5 km of the residences of the subjects and averaged over various lag

12 periods (1-24 h, 12 h and 24 h moving average [ma]) before the ECG. The final analyses included 24

13 subjects with 269 observations and results showed consistent negative associations of ST-segment level

14 with increased BC with the strongest association with the 5-h lag. CO during the same lag period also

15 showed a negative association with ST-segment depression, however only BC remained significant in

16 multipollutant models.

17   In summary, few studies have examined the effect of CO on HR and while two of the three studies

18 reported a positive association, further research is warranted to corroborate the current results. Similarly,

19 while a larger number of studies have examined the effect of CO on various HRV parameters, mixed

20 results have been reported throughout these studies. Furthermore, with several HRV parameters often

21 examined, there are mixed results across the studies as to the HRV parameters that are positively

22 associated with CO exposure. Table 5-4 shows a summary of the reviewed studies.

Table 5-4.   **Summary of studies investigating the effect of CO exposure on HRV parameters.**

Study	Location (Sample Size)	Cardiac Endpoint	Exposure Assessment	Mean CO Level (ppm)	Copollutants
Gold et al. (2000)	Boston, MA (n = 21)	HR, SDNN, r-MSSD	Ambient	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)	Boston, MA (n = 28)	SDNN, r-MSSD, PNN, LF/HF	Ambient	25th, 50th, 75th percentiles: 0.38, 0.45, 0.54	$PM_{2.5}$, BC, NO_2, O_3
Park et al. (2005b)	Boston, MA (n = 4 97)	SDNN, LF, HF, LF/HF	Ambient	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)	Mexico City, Mexico (n = 30)	HF, LF, VLF, HR, R-R	Personal	Mean: 2.9 (11 h) Range: 0.1-18	$PM_{2.5}$
Holguin et al. (2003)	Mexico City, Mexico (n = 34)	HF,Double check LF, LF/HF	Ambient	Mean: 3.3(24 h) Range: 1.8-4.8	$PM_{2.5}$, O_3, NO_2, SO_2

Study	Location (Sample Size)	Cardiac Endpoint	Exposure Assessment	Mean CO Level (ppm)	Copollutants
Wheeler et al. (2006)	Atlanta, GA (n = 30)	SDNN, r-MSSD, PNN, LF, HF, LF/HF	Ambient	Mean: 362 ppb (4h) 25th, 50th, 75th percentiles: 221.5, 304.3, 398.1	$PM_{2.5}$, O_3, NO_2, SO_2
Dales et al. (2004)	Toronto, Canada (n = 36)	SDNN, HF, LF, LF/HF, N-N	Personal	Mean: 2.4* Range: 0.4-16.5	$PM_{2.5}$
Peters et al. (1999a)	Augsburg, Germany (n = 2681)	HR	Ambient	Mean: 3.6 Range: 1.5-7.1	TSP, SO_2
Liao et al. (2004)	Maryland, North Carolina, Minnesota, (n = 4899-6784)	HR, SDNN, LF, HF	Ambient	Mean: 0.65 (24 h)	PM_{10}, O_3, NO_2, SO_2
Timonen et al. (2006)	Amsterdam, the Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	SDNN, HF, LF/HF	Ambient	Mean: 0.35-0.52 Range: 0.09-2.17	$PM_{2.5}$, PM_{10}, NO_2
Ibald-Mulli et al. (2004)	Amsterdam, the Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	BP, HR	Ambient	Mean: 0.35-0.52 Range: 0.09-2.17	UFP, PM_{10}, $PM_{2.5}$, NO_2, SO_2
Tarkiainen et al. (2003)	Kuopio, Finland (n = 6)	PNN, SDNN, r-MSSD	Personal	Mean: 4.6 Range: 0.5-27.4	None
Chan et al. (2005)	Taipei, Taiwan (n = 83)	SDNN, r-MSSD, LF	Ambient	Mean: 1.1 Range: 0.1-7.7	PM_{10}, NO_2, SO_2
Gold et al. (2005)	Boston, MA (n = 28)	ST-segment	Ambient	Median: 0.56 (12 h) Maximum: 1.04	$PM_{2.5}$, BC

*95th percentile of 24-h levels

Arrhythmia

1   Cardiac arrhythmia refers to a broad group of conditions where there is irregular electrical activity
2   in the heart. The main types of arrhythmias are fibrillation, tachycardia, and bradycardia, all of which can
3   be associated with the upper (atria) and lower (ventricle) chambers of the heart. Briefly, fibrillation refers
4   to when a chamber of the heart quivers chaotically rather than pumps in an orderly fashion, tachycardia
5   refers to a rapid heart beat (e.g., >100 beats/minute) while bradycardia refers to a slow heart beat
6   (e.g., <60 beats/minute). A few air pollution panel studies have examined the occurrence of cardiac
7   arrhythmias by analyzing data recorded by implantable cardioverter defibrillators (ICDs) among cardiac
8   patients. The majority of these studies were conducted in North America with the main outcome
9   investigated being tachycardia. Results of these studies provide little evidence for an association between
10   cardiac arrhythmia and ambient CO.
11   For example, Dockery and colleagues (2005) analyzed the relationship between ambient air
12   pollution and the daily incidence of ventricular tachyarrhythmia among 203 patients with ICDs in Boston,
13   MA. An hourly city average for the Boston metropolitan area was calculated for CO, O_3, NO_2, SO_2, SO_4^{2-},
14   BC, and $PM_{2.5}$. Although positive associations between ventricular arrhythmic episode days were found
15   for all mean pollutant levels on the same day and previous days, none of these associations approached
16   statistical significance. However, when the analyses were stratified by patients who had a previous

1	incidence of ventricular arrhythmia within 3 days, or greater than 3 days to the day of interest, a 0.5 ppm
2	increase in 24-h CO concentration was positively associated with incidence of ventricular arrhythmia
3	(OR: 1.68 [95% CI: 1.18-2.41) among those who had a ventricular arrhythmia within the last 3 days.
4	A similar study in eastern Massachusetts examined cardiac arrhythmia by analyzing defibrillator
5	discharges precipitated by either ventricular tachycardia or fibrillation among 100 cardiac patients (Peters
6	et al., 2000b). Exposure to ambient CO was estimated for the same day, 1-day, 2-day, 3-day, and a 5-day
7	mean lag period. Co was moderately correlated with PM_{10} (r = 0.51) and $PM_{2.5}$ (r = 0.56) and more highly
8	correlated with NO_2 (r = 0.71). When analyzing patients who had at least one defibrillator discharge
9	(n = 33) there was no association with CO. However, when analyzing patients who had at least 10
10	discharges (n = 6), a 0.5 ppm increase in 24-h CO concentration (lag 0-4) was associated with an
11	increased odds of a defibrillator discharge (OR: 1.66 [95% CI: 1.01-2.76]).
12	In contrast, other air pollution panel studies conducted in St Louis, MO (among 56 subjects) (Rich
13	et al., 2006b), Atlanta, GA (among 518 subjects) (Metzger et al., 2007), Boston, MA (among
14	203 subjects) (Rich et al., 2005), and Vancouver, Canada (Rich et al., 2004; Vedal et al., 2004) (among 34
15	and 50 subjects respectively) did not find an association between short term changes in ambient CO and
16	occurrence of cardiac arrhythmia in patients with implantable defibrillators. The study in Boston also
17	examined atrial fibrillation episodes among the same group of subjects and also did not find an
18	association with ambient CO (Rich et al., 2005).
19	An alternative method used to assess the relationship between cardiac arrhythmia and ambient air
20	pollution is to analyze cardiac data recorded via ECG. Two studies have employed this method and
21	reported inconsistent results. A study in Steubenville, OH, which is located in an industrial area, examined
22	weekly ECG data among 32 non-smoking older adults for 24 weeks during summer and fall (Sarnat et al.,
23	2006). Ambient exposures for up to 5 days prior to the health assessment (based on a 5-day moving
24	average) were calculated for $PM_{2.5}$, SO_4^{2-}, elemental carbon (EC), O_3, NO_2, SO_2, and CO from data
25	recorded at one central monitoring site. Increases in ambient CO were not associated with increased odds
26	of having at least one arrhythmia during the study period.
27	In contrast, a study in Germany examined the relationship between ambient air pollution and the
28	occurrence of supraventricular (atria) and ventricular tachycardia recorded via monthly 24-h ECGs among
29	57 subjects over a 6 month period (Berger et al., 2006). Exposure estimates were calculated for ambient
30	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,
31	72-95 h, and 5-day avg) prior to the ECG. Results showed that a 0.5 ppm increase in ambient 24-h CO
32	concentration (lag 0-4 days prior to ECG) was positively associated with the occurrence of
33	supraventricular tachycardia (OR: 1.36 [95% CI: 1.08-1.74]). However, ambient CO was not associated
34	with ventricular tachycardia.
35	In summary, few studies have examined associations between CO and the occurrence of cardiac
36	arrhythmias, and these studies provided little evidence of a CO effect on cardiac arrhythmias. While more

1 studies analyzed data from ICDs, very few reported significant associations. This was similar for the

2 mixed results from the two studies that analyzed ECG data to evaluate cardiac arrhythmias in association

3 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	Exposure Assessment	Mean CO Level (ppm)	Copollutants
ARRHYTHMIAS (AMONG PATIENTS WITH ICDS)					
Dockery et al. (2005)	Boston, MA (n = 203)	Ventricular Tachycardia	Ambient	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. (2000b)	Massachusetts, (n = 100)	Ventricular fibrillation or tachycardia	Ambient	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. (2006b)	Boston, MA (n = 56)	Ventricular arrhythmia	Ambient	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)	Atlanta, GA (n = 518)	Ventricular Tachycardia	Ambient	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)	Boston, MA (n = 203)	Atrial fibrillation	Ambient	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)	Vancouver, Canada (n = 34)	ICD discharge due to arrhythmia	Ambient	Mean: 0.55 (24 h) IQR: 0.16	$PM_{2.5}$, PM_{10}, EC, O_3, NO_2, SO_2, SO_4
Vedal et al. (2004)	Vancouver, Canada (n = 50)	ICD discharge due to arrhythmia	Ambient	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)	Steubenville, OH (n = 32)	Atrial or ventricular tachycardia	Ambient	Mean: 0.2 (24 h) Range: 0.1, 1.5	$PM_{2.5}$, O_3, NO_2, SO_2, SO_4, EC
Berger et al. (2006)	Erfurt, Germany (n = 57)	Atrial or ventricular tachycardia	Ambient	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

Cardiac Arrest

4 Cardiac arrest refers to the abrupt loss of heart function due to failure of the heart to contract

5 effectively during systole, which can lead to sudden cardiac death if not treated immediately. Very few

6 studies have investigated the association between ambient CO exposure and the risk of cardiac arrest and

7 none reported a significant link between increased CO exposure and the occurrence of cardiac arrest.

1   Two similar studies were conducted in Seattle, WA, and both did not report an association between

2   ambient CO and cardiac arrest. Both studies employed a case-crossover design and examined air pollution

3   exposures for black smoke particles (BSP), PM_{10}, SO_2, and CO. The correlation coefficient for PM_{10} and

4   CO was 0.81. The first of these studies examined paramedic-attended out-of-hospital primary cardiac

5   arrests among 362 cases (between 1998-1994) in Seattle and King County, WA whereby lags of 0-5 days

6   were analyzed (Levy et al., 2001). The second of these studies examined out-of-hospital primary cardiac

7   arrest for a ten year period (1985-1994) among subjects within a health organization database (the Group

8   Health Cooperative of Puget Sound) whereby 0-day through 2-day lags were analyzed (Sullivan et al.,

9   2003).

Myocardial Infarction

10   As previously stated, MI is commonly referred to as 'heart attack' and is another cardiac outcome

11   that has received limited attention within the area of air pollution research. Only one study has

12   investigated the association between short-term changes in ambient CO and the onset of MI. Peters and

13   colleagues (2001) employed a case-crossover study design to analyze short term exposures (0-5 h and 0-

14   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)

15   among 772 patients with MI in the greater Boston area. While all pollutants showed positive associations

16   with the onset of MI, only $PM_{2.5}$ reached statistical significance with the main exposure period being 2 h

17   before the onset.

Blood Pressure

18   Only two studies have investigated whether short-term ambient CO influences BP. The earlier of

19   these two studies examined BP among 2607 men and women aged 25-64 who participated in the

20   Augsburg, Germany MONICA study (Ibald-Mulli et al., 2001). Exposures to ambient TSP, SO_2 and CO

21   (from one monitor in the center of the city) during the same day as the BP reading and an average over the

22   5 days prior were examined. Results showed that ambient CO had no association with BP.

23   Similarly, the second of these studies extracted baseline and repeated-measures of cardiac

24   rehabilitation data from a Boston, MA hospital for 62 subjects with 631 visits and analyzed ambient air

25   pollution exposures (with particular focus on $PM_{2.5}$) averaged over various periods up to 5 days before the

26   visit (Zanobetti et al., 2004b). While results showed significant associations between increased BP and

27   ambient $PM_{2.5}$, SO_2, O_3, and BC, there was no significant effect for CO.

Blood Markers of Coagulation and Inflammation

28   Several studies have investigated the association between ambient CO and various blood markers

29   related to coagulation and inflammation. The main endpoints analyzed have been plasma fibrinogen,

1   Factor VII, C-reactive protein (CRP), prothrombin, intercellular adhesion molecule (ICAM-1), and white
2   blood cell count (WBC).
3   Pekkanen et al. (2000) examined the association between daily concentrations of air pollution and
4   concentrations of plasma fibrinogen measured among 4982 male and 2223 female office workers in
5   Whitehall, London, U.K. between September 1991 and May 1993. Plasma fibrinogen data were linked to
6   ambient exposure to BS, PM_{10}, O_3, NO_2, SO_2, and CO, where the exposures were derived from data
7   recorded at 5 fixed sites across London. There was a high correlation between levels of CO and NO_2
8   ($r = 0.81$) and more moderate correlations with PM_{10} ($r = 0.57$) and SO_2 ($r = 0.61$). The pollution data on
9   the same day when the blood sampling was done (lag 0) and on the 3 previous days (lags 1-3) were
10   analyzed. Results showed that ambient CO at all lags was significantly associated with an increase in
11   plasma fibrinogen. Results were similar for NO_2 while all other pollutants were not associated with an
12   increase in plasma fibrinogen.
13   Liao et al. (2005) examined associations between various air pollutants and hemostatic and
14   inflammatory markers (fibrinogen, factor VIII-C, von Willebrand factor, serum albumin, WBC) among
15   10,208 middle-aged males and females from the ARIC study. Exposure estimates for ambient PM_{10}, NO_2,
16   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
17   CO concentration was significantly associated with 0.015 g/dL decrease in serum albumin among persons
18   with a history of CVD. CO was not associated with other hemostatic or inflammatory factors.
19   In Israel, Steinvil et al. (2008) examined WBC, fibrinogen, and CRP among 3,659 study subjects
20   enrolled in the Tel-Aviv Sourasky Medical Center inflammation survey, in which subjects lived <11km
21   from an ambient air pollution monitor. Air pollution data in the form of PM_{10}, NO_2, SO_2, O_3, and CO were
22   derived from data recorded at fixed sites. The correlations coefficients were high between CO and NO_2
23   ($r = 0.86$) and PM_{10} ($r = 0.75$). Exposures for lag days 1-7 were analyzed and ambient CO had a
24   significant negative effect on fibrinogen only among males. Significant associations were reported for lag
25   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
26   0.5 ppm increase in 24-h CO concentration. A similar negative effect for CO was observed on WBC
27   among males only. The average CO exposure over the week prior to the sampling yielded the largest
28   reduction in WBC (-263 cells/μL).
29   In a German study, Rückerl and colleagues (2006) recruited 57 non-smoking male patients with
30   CHD who were scheduled for 12 subsequent clinical visits where samples of blood were collected. The
31   authors tested the primary hypothesis that CRP would increase in association with a rise in air pollution
32   levels. CRP is an acute phase protein that increases during inflammatory processes in the body. Other
33   markers of inflammation (serum amyloid A [SAA]), cell adhesion (E-selectin, von Willebrand factor
34   antigen [vWF], ICAM-1), and coagulation (fibrinogen, factor VII [FVII], prothrombin fragment 1+2)
35   were also examined. Ambient air pollution in the form of PM_{10}, ultrafine particles (UFP), EC, NO_2, and
36   CO was monitored at one central site and a 24-h avg immediately preceding the clinic visit (lag 0) and up

1   to 5 days (lags 1-4) was calculated for each patient. For CRP, the odds of observing CRP concentrations

2   above the 90th percentile were 2.41 (95% CI: 1.23-5.02) in association with a 0.5 ppm increase in 24-h

3   CO concentration (lag 2). CO concentration during lags 1 and 2 was associated with observing ICAM-1

4   concentrations above the 90th percentile (OR: 2.41 [95% CI: 1.49-4.04]; OR: 3.17 [95% CI: 1.77-6.11],

5   respectively). CO concentration during lags 0-3 was associated with a decrease in FVII.

6   A similar study by Ruckerl and colleagues (2007) was conducted among 1,003 MI survivors across

7   6 European cities (Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome,

8   Italy; Stockholm, Sweden). The study compared repeated measurements of interleukin-6 (IL-6), CRP and

9   fibrinogen with concurrent ambient levels of air pollution (particle number count [PNC], PM_{10}, $PM_{2.5}$,

10 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

11 sampling were analyzed and ambient CO was not associated with any of the inflammatory endpoints.

12   Baccarelli et al. (2007) recruited 1,218 healthy individuals from the Lombardia region in Italy and

13 assessed whether blood coagulability is associated with ambient air pollution. The main blood

14 coagulability endpoints of interest were prothrombin time (PT) and activated partial thromboplastin time

15 (APTT), which are measures of the quality of the coagulation pathways, assuming that, if shortened these

16 measures would reflect hypercoagulability. Air pollution data (PM_{10}, O_3, NO_2, and CO) were obtained

17 from 53 fixed stations across the Lombardia region, which was divided into nine different study areas and

18 a network average for each pollutant was calculated across the available monitors within each of the nine

19 study areas. The analyses examined air pollution at the time of the blood sampling as well as averages for

20 the 7 days prior and 30 days prior. Results showed that ambient CO at the time of blood sampling was

21 associated with a decrease in PT (coefficient = -0.11 [95% CI: -0.18 to -0.05, p <0.001), indicating

22 hypercoagulability. However, PM_{10} and NO_2 at the time of blood sampling were also associated with a

23 decrease in PT and results from multipollutant models were not reported. Acute phase reactants such as

24 fibrinogen, and naturally occurring anticoagulants such as antithrombin, protein C and protein S were

25 examined and none were associated with ambient air pollution.

26   In summary, despite the small number of studies, there was some evidence of a significant link

27 between CO exposure and blood markers of coagulation and inflammation. Table 5.6 summarizes the

28 reviewed studies.

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	Exposure Assessment	Mean CO Level (ppm)	Copollutants
Pekkanen et al (2000)	London, U.K. (n = 7205)	Plasma fibrinogen	Ambient	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)	USA (n = 10.208)	Fibrinogen, VII-C, WBC, albumin, vWF	Ambient	Mean: 1.4 (24 h)	PM_{10}, O_3, NO_2, SO_2
Steinvil et al (2008)	Tel-Aviv, Israel (n = 3659)	CRP, fibrinogen, WBC	Ambient	Mean: 0.8 25th, 50th, 75th percentiles: 0.7, 0.8, 1.0	PM_{10}, O_3, NO_2, SO_2
Ruckerl et al (2006)	Erfurt, Germany (n = 57)	CRP, SAA, cell adhesions and coagulation	Ambient	Mean: 0.45 (24 h) Range: 0.10, 1.68	PM_{10}, $PM_{2.5}$, UFP, EC, NO_2
Rukerl et al (2007)	Six European cities (n = 1003)	IL-6, CRP, fibrinogen	Ambient	Mean (24 h): 0.29-1.48	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Baccarelli et al (2007)	Lombardia region, Italy (n = 1218)	PT, APTT, fibrinogen, anticoagulants	Ambient	Mean: 1.14-3.11 Max: 5.52-11.43	PM_{10}, O_3, NO_2, SO_2

Hospital Admissions and Emergency Department Visits

1   Since the 2000 CO AQCD there have been a number of studies investigating the effect of ambient
2   CO on hospital admissions and ED visits for cardiovascular diseases. Some of these studies have focused
3   solely on one specific CVD outcome, and these studies are discussed first. This is followed by a
4   discussion of studies that investigated admissions for all CVD outcomes (e.g., non-specific) or a variety
5   of specific CVD outcomes.

Ischemic Heart Disease, Myocardial Infarction, and Angina Pectoris

6   Ischemic heart disease (IHD), also known as coronary heart disease (CHD), is caused by
7   inadequate circulation of the blood to the heart muscle, which is a result of the heart arteries being
8   blocked by cholesterol deposits. IHD can lead to sudden episodes such as MI ("heart attack") or death, as
9   well as chronic conditions such as angina pectoris (chest pain).
10   **Ischemic Heart Disease.** Very few studies have focused directly on hospitalizations for IHD.
11   There is a lot of variation among these studies with regard to methods employed and results reported. It
12   should be noted that within these studies IHD included MI and angina pectoris (ICD-9 codes 410-414;
13   ICD-10 codes 120, 121-123, 124). Mann and colleagues (2002) investigated the modifying effect of
14   secondary diagnosis of arrhythmia and congestive heart failure (CHF) on the relationship between
15   hospital admissions for IHD (ICD-9: 410-414) and ambient air pollutants for the period of 1988 to 1995
16   in southern California. There were 54,863 visits analyzed and a 0.75 ppm increase in 8-h max CO

1   concentration was associated with a 2.69% (95% CI: 1.21-4.19) increase in same-day IHD admissions

2   among persons with a secondary diagnosis of CHF, a 2.23% (95% CI: 1.35-3.13) increase among persons

3   with a secondary diagnosis of arrhythmia, and a 1.21% (95% CI: 0.49-1.94) among persons without either

4   secondary diagnosis. Of all pollutants examined (PM_{10}, NO_2, O_3, CO), only NO_2 showed similar positive

5   effects to CO and no multipollutant models were analyzed. The correlation coefficients between CO and

6   NO_2 ranged from 0.64 to 0.86 across the seven regions. This study indicated that people with IHD and

7   accompanying CHF and /or arrhythmia are a sensitive group in relation to the effects of ambient air

8   pollution.

9   By using a time-series approach, ED visits for IHD (ICD-9: 410-414) in Montreal, Canada

10   (1997-2002) were examined in relation to ambient CO concentrations (lags 0 and 1) (Szyszkowicz, 2007).

11   A total of 4,979 visits were analyzed and results showed significant positive effects with a 0.5 ppm

12   increase in 24-h CO concentration (lag 0) attributing to a 14.1% (95% CI: 5.8-20.6) increase in daily ED

13   visits among all patients. Stratified analyses showed that this effect was mostly among male patients

14   (19.8% [95% CI: 9.2-31.6]). NO_2 was the only other pollutant examined, and it too showed significant

15   positive associations with ED visits for IHD for same-day exposure; however, no multipollutant models

16   were examined.

17   Lee and colleagues (2003b) examined daily counts of hospital admissions for IHD in Seoul, Korea

18   for the period from December 1997 to December 1999. Single-day lags 0 to 5 were analyzed and the lag

19   period with the strongest association for each pollutant was chosen. For CO, lag 5 showed the strongest

20   effect with a 1 ppm increase in 1-h maximum (max) CO concentration associated with a daily increase in

21   the number of hospital admissions for IHD; however, this was only among patients 64+ years of age (RR:

22   1.07 [95% CI: 1.01-1.13]). All other pollutants (PM_{10}, O_3, NO_2) except SO_2 showed similar significant

23   effects and in a two-pollutant model with PM_{10} the CO effect attenuated toward the null.

24   Other studies have examined hospital admissions for IHD while investigating a broad group of

25   CVD outcomes. A study was conducted in Atlanta, GA, where over 4 million ED visits from 31 hospitals

26   for the period 1993 to 2000 were analyzed (Study of Particles and Health in Atlanta [SOPHIA]). Several

27   articles have been published from this research with two examining cardiovascular admissions in relation

28   to CO concentrations. The first of these (Metzger et al., 2004a) used a time-series design and analyzed a

29   3-day moving average over single-day lags 0-2 as the a priori lag structure. Although of borderline

30   statistical significance, CO was positively associated with an increase in ED visits for IHD (RR 1.016

31   [95% CI: 0.999-1.034] per 1 ppm increase in 1-h max CO concentration).

32   The second of these reports (Peel et al., 2007) examined the association of ambient air pollution

33   levels and cardiovascular morbidity in visits with and without specific secondary conditions (e.g., co-

34   morbidity). Within a time-stratified case-crossover design using the same lag structure already mentioned,

35   the main results showed that a 1 ppm increase in 1-h max CO concentration was associated with an

1   increase in IHD among those without diabetes (OR: 1.023 [95% CI: 1.004-1.042]), and without CHF

2   (OR: 1.024 [95% CI: 1.006-1.042]).

3   Two Australian studies have also examined associations between ambient CO concentrations and

4   increased hospital admissions for various CVD outcomes. The first of these studies (Barnett et al., 2006)

5   analyzed data from 5 of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and

6   two New Zealand cities (Auckland, Christchurch) for the period 1998-2001. A time-stratified case-

7   crossover design was employed and the age groups of 15-64 years and $\geq$ 65 years were analyzed for the

8   0-1 lag period. The pooled estimates across all cities showed that a 0.75 ppm increase in 8-h max CO

9   concentration was associated with a 1.9% (95% CI: 0.7-3.2) increase in admissions for IHD, but only

10   among the elderly group ($\geq$ 65 years).

11   The second of the Australian studies (Jalaludin et al., 2006) examined ED visits for CVD outcomes

12   in the elderly (65+ years) in Sydney for the period 1997 to 2001. Using a time-series approach, single-day

13   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

14   concentration (lag 0) was associated with increases in IHD emergency department visits of 3.1%

15   (95% CI: 1.3-4.9).

16   **Myocardial Infarction.** Linn et al. (2000) examined the association between ambient air pollution

17   and hospital admissions for cardiopulmonary illnesses in metropolitan Los Angeles for the years

18   1992-1995. Using a time-series approach, a 0.5 ppm increase in same-day 24-h avg CO concentration was

19   associated with a 2.0% increase in MI hospital admissions among people aged >30 years. When the

20   analyses were stratified by season, no significant effects were observed (No quantitative seasonal effects

21   reported). A time-series study in Denver, Colorado, investigated daily hospital admissions for various

22   CVD outcomes among older adults (>65 years) across 11 hospitals (Koken et al., 2003). Data between

23   July and August for the period 1993-1997 were analyzed. Single-day lags 0 to 4 were examined and CO

24   showed no association with hospital admissions for MI (quantitative results were not reported).

25   As part of the HEAPSS (Health Effects of Air Pollution among Susceptible Subpopulations) study,

26   Lanki et al. (2006) investigated the association between traffic-related exposure to air pollutants and

27   hospitalization for first acute myocardial infarction (AMI). Data were collected from five European cities

28   with either AMI registers (Augsburg, Barcelona), or hospital discharge registers (Helsinki, Rome,

29   Stockholm). Correlation coefficients between CO and NO_2 ranged from 0.43 to 0.75 across the five cities,

30   and for PM_{10} the range was 0.21 to 0.56. A total of 26,854 hospitalizations were analyzed and pooled

31   estimates from all 5 cities showed that there was a weak positive association with AMI hospitalizations

32   and 24-h avg CO concentrations at lag 0 (RR: 1.014 [95% CI: 1.000-1.029] per 0.5 ppm increase), but

33   more so when only using data from the three cites (Helsinki, Rome, Stockholm) with hospital discharge

34   registers (RR: 1.020 [95% CI: 1.003-1.035] per 0.5 ppm increase). When analyses were stratified by

35   fatality and age, results showed that the CO effect was significantly associated with fatal AMI among the

1 <75-year age group (RR: 1.080 [95% CI: 1.017-1.144), and with non-fatal AMI in the ≥ 75-year age

2 group (RR: 1.044 [95% CI: 1.011-1.076).

3   Further analyses within the HEAPSS cohort was conducted where the event of cardiac readmission

4 among the first MI survivors (n = 22, 006) was linked to ambient air pollution (von Klot et al., 2005). The

5 readmissions of interest were those with primary diagnosis of AMI, angina pectoris, dysrhythmia, and

6 heart failure that occurred at least 29 days after the index event. Single-day lags 0 to 3 were examined and

7 pooled estimates from all 5 cities showed that a 0.5 ppm increase in same-day (lag 0) CO was associated

8 with an increase in cardiac (e.g., any of the diagnoses) readmissions (RR: 1.041 [95% CI: 1.003-1.076])

9 and this persisted in two-pollutant models that included either PM_{10} or O_3. Correlation coefficients with

10 CO ranged from 0.21 to 0.57 for PM_{10} and 0.44 to 0.75 for NO_2.

11   A study in Rome, Italy, also found an association between ambient CO and hospitalizations for first

12 episode MI among 6,531 subjects (January 1995-June 1997) (D'Ippoliti et al., 2003). A case-crossover

13 design with stratification of time into separate months was used to select referent days as the days falling

14 on the same day of the week within the same month as the index day. CO concentration was positively

15 associated for lag 2 (OR: 1.019 [95% CI: 1.001-1.037]). The other pollutants analyzed were NO_2 and TSP,

16 both of which exhibited a significant positive effect at lag 0. TSP also showed a significant positive effect

17 at lag 0-2 and when entered into a model with CO, the CO effect did not persist.

18   The previously mentioned Australian and New Zealand study that analyzed data from seven cities

19 (Brisbane, Canberra, Melbourne, Perth, Sydney, Auckland, and Christchurch) for the period 1998-2001

20 also reported an association between CO and MI hospitalization (Barnett et al., 2006). The pooled

21 estimates across all cities showed that a 0.75 ppm increase in 8-h max CO concentration was associated

22 with a 2.4% (95% CI: 0.6-4.1) increase in admissions for MI, but only among older adults (≥ 65 years).

23   **Angina Pectoris.** In the current literature, only one study was identified that focused solely on

24 angina pectoris as an endpoint. Admissions data for angina pectoris were collected from 25 academic

25 hospitals in Tehran, Iran, and linked to ambient air pollution for the period of 1996 to 2001 (Hosseinpoor

26 et al., 2005). Using a time-series approach, single-day lags of 0 to 3 were analyzed and a 0.5 ppm increase

27 in 24-h avg CO concentration at lag 1 was associated with increased hospital admissions for angina (OR:

28 1.005 [95% CI: 1.003-1.007). This result persisted in a multipollutant model that also included NO_2,

29 PM_{10}, and O_3 with CO being the only significant pollutant (OR: 1.005 [95% CI: 1.001-1.008]).Figure 5-1

30 shows the effect estimates associated with daily admissions for various forms of IHD from selected

31 studies. Table 5.7 shows a summary of the IHD hospital admission studies that examined CO exposures.

32   In summary, the majority of studies reported significant increases in the daily number of

33 admissions for IHD and MI in relation to CO exposures. In studies that stratified by age groups and/or

34 sex, the effects were larger among the elderly and males. Among the different lag periods being

35 examined, the associations were more commonly observed with same day CO (lag 0) or an average over

36 the same day and previous day (lag 0-1).
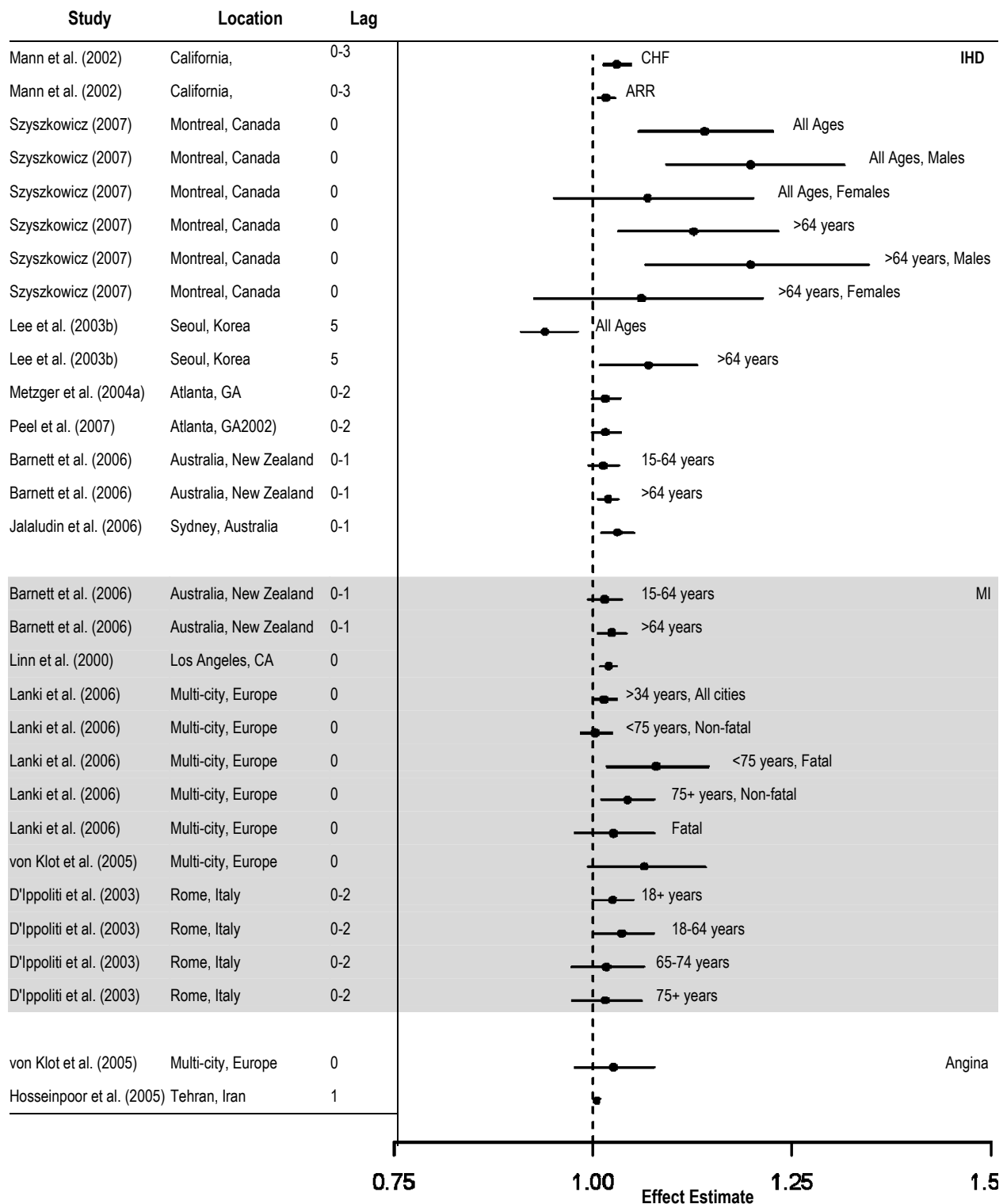
Figure 5-1. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for various froms of IHD. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-7. Summary of IHD hospital admission studies.[1]

Study	Location	Endpoints Examined	Copollutants	Lags Examined	CO Levels (ppm)
STUDIES THAT FOCUSED SOLELY ON IHD, MI, OR ANGINA					
Mann et al. (2002)	Southern California (1988-1995)	IHD	PM_{10}, NO_2, O_3	0,1,2, 2-4ma	Mean: 2.07 (8h)
Szyszkowicz (2007)	Montreal, Canada (1997-2002)	IHD	NO_2	0,1	Mean: 0.5 (24 h)
Lee et al. (2003b)	Seoul, Korea (1997-1999)	IHD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4,5	Mean: 1.8
Lanki et al. (2006)[2]	5 European cities (1992-2000)	MI (first acute)	PM_{10}, NO_2, O_3, PNC	0,1,2,3	Highest city was Rome. 25th = 1.5 75th = 2.9 mg/m^3
von Klot et al. (2005)[2]	5 European cities (1992-2001)	MI, Angina, Cardiac*	PM_{10}, NO_2, O_3, PNC	0,1,2,3	Mean: highest city was Rome: 1.9 (24 h)
D'Ippoliti et al. (2003)[2]	Rome, Italy (1995-1997)	MI	TSP, NO_2, SO_2	0,1,2,3,4, 0-2	Mean: 3.8 (24 h)
Hosseinpoor et al. (2005)[2]	Tehran, Iran (1996-2001)	Angina	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	Mean: 9.4 (24 h)
STUDIES THAT EXAMINED IHD, MI, OR ANGINA AMONG OTHER CVDS					
Metzger et al. (2004a)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean: 1.5 (1 h)
Peel et al. (2007)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean: 1.5 (1 h)
Barnett et al. (2006)	Australia and New Zealand (1998-2001)	IHD, MI, All CVD, CA, Stroke	PM_{10}, NO_2, O_3	Lag 0-1	Mean: (8 h) 0.5- 2.1
Jalaludin et al. (2006)	Sydney, Australia (1997-2001)	IHD, All CVD, Stroke, Cardiac	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	Mean: 0.82 (8 h)
Linn et al. (2000)	Los Angeles, CA (1992-1995)	MI, All CVD, CHF, CA, OS	PM_{10}, NO_2, O_3	0	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Koken et al. (2003)	Denver, CO (1993-1997)	MI, CAth, PHD, CD, CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4	Mean: 0.9 ppm (24 h)

[1]Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhthmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.

[2] 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 tempterature.

Stroke

1   A stroke is the result of either the blood supply to the brain being blocked (e.g., embolism), which

2 refers to an ischemic stroke (80% of strokes), or the occurrence of a burst blood vessel or hemorrhaging,

3 referred to as a hemorrhagic stroke. Hemorrhagic stroke has two main groupings; intracerebral

4 hemorrhagic stroke (10% of strokes), which is when a blood vessel in the brain leaks, and subarachnoid

5 hemorrhage (3% of strokes), which is bleeding under the outer membranes of the brain. The third type of

6 stroke is a transient ischemic attack (TIA), or mini–stroke, which has the same early symptoms as a

7 normal stroke but the symptoms disappear within 24 hours, leaving no apparent deficits.

8   A small number of air pollution studies have investigated hospital admissions for the three main

9 forms of stroke with the majority reporting positive associations with ambient CO and lag periods

10 between 0 and 3 days.

11   A U.S. study across 9 cities investigated hospital admissions for ischemic and hemorrhagic stroke

12 among Medicare beneficiaries aged 65+ years of age (155,503 ischemic and 19,314 hemorrhagic

13 admissions from the ED) (Wellenius et al., 2005a). Single-day lags 0 to 2 were examined and based on a

14 pooled estimate, same-day CO (lag 0) was associated with an increase in admissions of 1.98%

15 (95% CI: 0.86-3.12) per 0.5 ppm increase in 24-h CO concentration) for ischemic stroke admissions but

16 not hemorrhagic stroke admissions (-1.14%, 95% CI: -3.40 to 1.18). All other pollutants examined (PM_{10},

17 NO_2, SO_2) were associated with an increase in ischemic stroke admissions, but not hemorrhagic stroke

18 admissions.

19   Villeneuve and colleagues (2006a) studied ED visits for hemorrhagic strokes, acute ischemic

20 strokes and transient ischemic attacks among individuals 65+ years of age at 5 hospitals within the

21 Edmonton area in Canada between April 1992 and March 2002 (12,422 visits). Within a time-stratified

22 case-crossover design the analyses were stratified by two seasonal groups (October-March and April-

23 September) and CO only had an effect on ischemic stroke during April-September. A 0.5 ppm increase the

24 CO concentration for a 3-day avg across lags 0-2 was associated with a 32% increase in risk (OR: 1.32

25 [95% CI 1.09-1.60]). CO had no effect on any other stroke subtype. In two-pollutant models the CO effect

26 on ischemic stroke persisted after controlling for PM_{10}, $PM_{2.5}$, SO_2, and O_3. When all seasons and all

27 strokes were combined there was no statistically significant association between all the pollutants

28 examined and increased admissions for stroke.

29   In Kaohsiung City, Taiwan, CO averaged over lags 0-2 was associated with increased admissions

30 for stroke across 63 hospitals (Tsai et al., 2003b). From 1997 to 2000 a total of 23,179 admissions were

31 analyzed and on warm days (≥ 20°C) the odds ratios for primary intracerebral hemorrhage and ischemic

32 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

33 24-h CO concentration. For the same increase in CO on cool days (<20°C) the odds ratios were 1.33

34 (95% CI: 0.38-2.55) for intracerebral hemorrhage and 2.68 (95% CI: 1.59-4.49) for ischemic stroke.

1   These results persisted in two-pollutant models that included PM_{10}, SO_2, and O_3, but did not persist when

2   controlling for NO_2.

3   Earlier research conducted in metropolitan Los Angeles examined hospital admissions for

4   cardiopulmonary illnesses from 1992-1995 (Linn et al., 2000). Using a time-series approach, a 0.5 ppm

5   increase in 24-h CO concentration (lag 0) was associated with a 2.18% (95% CI: 1.73-2.62) increase in

6   occlusive (ischemic) stroke hospital admissions among people aged >30 years. When the analyses were

7   stratified by season there was a 1.8% increase during winter, a 4.55% increase during summer, and a 1.6%

8   increase during fall (results for spring were not reported).

9   A study in Taipei, Taiwan analyzed 8,582 emergency admissions for cerebrovascular diseases,

10   hemorrhagic stroke, ischemic stroke, and all strokes during 1997 to 2002 (Chan et al., 2006). Single-day

11   lags 0 to 3 were analyzed and a 0.75 ppm increase in 8-h max CO concentration (lag 2) was associated

12   with an increase in cerebrovascular diseases (OR: 1.03 [95% CI: 1.01-1.05]) and all strokes (OR: 1.03

13   [95% CI: 1.01-1.05]). These results persisted in two- and three-pollutant models that included O_3 and

14   PM_{10}. There was no association with individual ischemic or hemorrhagic stroke. CO was moderately

15   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).

16   The only time-series study that focused specifically on stroke hospital admissions that did not

17   report a significant association with ambient CO was conducted in Dijon, France (Henrotin et al., 2007).

18   Hospital admissions for different types of first-ever stroke (e.g., ischemic, hemorrhagic) among subjects

19   over 40 years of age were analyzed for the period of 1994 to 2004. A bi-directional case-crossover study

20   design was employed where single-day lags of 0 to 3 were examined and CO had no significant

21   association across all lags. This was also the case when the analyses were stratified by gender and types

22   of ischemic stroke (large arteries, lacunar, cardioembolic, transient). Of all pollutants examined (PM_{10},

23   NO_X, O_3, SO_2, CO) only O_3 showed a significant effect.

24   Two Australian studies examined associations between ambient CO and hospital admissions for

25   various CVDs. The first of these studies analyzed data from five of the largest cities in Australia

26   (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch)

27   for the period 1998-2001 (Barnett et al., 2006). A time-stratified case-crossover design was employed and

28   the age groups of 15-64 years and $\geq$ 65 years were analyzed for the 0-1 lag period (average over lag 0 and

29   1). The pooled estimates across all cities showed that CO had no effect on stroke admissions (quantitative

30   results not reported).

31   The second of the Australian studies examined ED visits for CVDs in older adults (65+ years) in

32   Sydney for the period from 1997 to 2001 (Jalaludin et al., 2006). Using a time-series approach, single-day

33   lags of 0 to 3 and an average over lags 0 and 1 (e.g., lag 0-1) were examined and CO showed no effect on

34   stroke ED visits. When the analyses were stratified by cool and warm periods a 0.75 ppm increase in 8-h

35   max CO concentration during the cool period was associated with a 3.8% (95% CI: 0.76-6.94) increase in

36   stroke ED visits.

1   Figure 5-2 shows the effect estimates associated with daily admissions for stroke from selected

2   studies. Table 5-8 shows a summary of the stroke hospital admission studies that examined CO exposures.

3   In summary, there was some evidence that increased ambient CO concentrations were associated

4   with an increase in the number of hospital admissions for stroke. The largest positive effects came from

5   the Taiwan study in Kaohsiung (Tsai et al., 2003b) with slightly larger effects during the warmer period

6   (>20°C). Similarly, in the Canadian study by Villeneuve and colleagues (2006a) there was a stronger

7   effect during the warmer period (April-September).

Study	Location	Lag
Wellenius et al. (2005a)	Multi-city, U.S.	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Tsai et al. (2003b)	Kaohsiung, Taiwan	0-2
Tsai et al. (2003b)	Kaohsiung, Taiwan	0-2
Linn et al. (2000)	Los Angeles, CA	0
Chan et al. (2006)	Taipei, Taiwan	1
Henrotin et al. (2007)	Dijon, France	3
Wellenius et al. (2005a)	Multi-city, U.S.	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Villeneuve et al. (2006a)	Edmonton, Canada	0-2
Tsai et al. (2003b)	Kaohsiung, Taiwan	0-2
Tsai et al. (2003b)	Kaohsiung, Taiwan	0-2
Chan et al. (2006)	Taipei, Taiwan	1
Henrotin et al. (2007)	Dijon, France	1
Chan et al. (2006)	Taipei, Taiwan	2
Jalaludin et al. (2006)	Sydney, Australia	0-1

IS= Ischemic Stroke, CIS=Cerebral Ischemic Stroke

Figure 5-2.   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.

Table 5-8.   Summary of stroke hospital admission studies.[1]

Study	Location	Type Of Stroke Examined	Copollutants	Lags Examined	CO Levels (ppm)
STUDIES THAT FOCUSED SOLELY ON STROKE					
Wellenius et al. (2005a)	9 cities, USA (1993-1999)	Isch, Hem	PM_{10}, NO_2, SO_2	0,1, 2	25th, 50th, 75th percentiles: 0.73, 1.02, 1.44
Villeneuve et al. (2006a)	Edmonton, Canada (1992-2002)	Isch, Hem, TIA	NO_2, SO_2, O_3	0,1, 0-2	Mean: 0.8 (24 h)
Tsai et al. (2003b)	Kaohsiung, Taiwan (1997-2000)	Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0-2	Mean: 0.79 (24 h)
Chan et al. (2006)	Taipei, Taiwan (1997-2002)	All, Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	Mean: 1.7 (8h)
Henrotin et al. (2007)[2]	Dijon, France (1994-2004)	Isch, Hem	PM_{10}, NO_X, SO_2, O_3	0,1,2,3	Mean: 0.59 (24 h)
STUDIES THAT EXAMINED STROKE AMONG OTHER CVDS					
Linn et al. (2000)	Los Angeles, CA (1992-1995)	Isch	PM_{10}, NO_2, O_3	Lag 0	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Barnett et al. (2006)	Australia and New Zealand (1998-2001)	All	PM_{10}, NO_2, O_3	Lag 0-1	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006)	Sydney, Australia (1997-2001)	All	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	Mean: 0.82 (8h)

[1] Isch = Ischemic; Hem = Hemorrhagic; TIA = transient ischemic attack
[2] 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 tempterature.

Congestive Heart Failure

1   Heart failure (HF) is a condition in which the heart is unable to adequately pump blood to the rest

2   of the body. It does not refer to the cessation of the heart, but more to the inability of the heart to operate

3   at an optimal capacity. HF is often called congestive heart failure (CHF), which refers to when the

4   inadequate pumping leads to a buildup of fluid in the tissues. The underlying causes of CHF are

5   hypertension, CAD, MI, and diabetes.

6   Wellenius and colleagues (2005b) examined the rate of hospitalization for CHF among 55,019

7   Medicare recipients (aged $\geq$ 65 years) residing in Allegheny County, PA, during 1987-1999. A time-

8   stratified case-crossover design was employed and single-day lags of 0 to 3 were analyzed and a 1 ppm

9   increase in 1-h max CO concentration on the same-day (lag 0) was associated with a 9.31%

10   (95% CI: 6.77-11.92) increase in the rate of hospitalization for CHF. This result persisted in two-pollutant

11   models that included PM_{10}, NO_2, O_3, and SO_2. CO was moderately correlated with SO_2 (r = 0.54) and

12   PM_{10} (r = 0.57) and more highly correlated with NO_2 (r = 0.70).

13   Another U.S. study recruited 125 patients diagnosed with CHF who were admitted to Johns

14   Hopkins Bayview Medical Center in Baltimore, MD (Symons et al., 2006). The patients were interviewed

15   after admission through the ED during their stays in overnight wards. The interview was designed to

1   collect information about symptom onset, health conditions, and factors related to air pollution exposure.

2   Various lag periods (single day and cumulative days 0 to 3) prior to the onset of symptoms were analyzed

3   and although the focus of this study was exposure to $PM_{2.5}$, of all the pollutants examined ($PM_{2.5}$, CO,

4   NO_2, O_3) only 8-h max CO concentration at lag 2 was significantly associated with the onset of CHF

5   symptoms (OR: 1.68 [95% CI: 1.28- 2.80]).

6   Earlier research conducted in metropolitan Los Angeles, CA examined hospital admissions for

7   cardiopulmonary illnesses 1992-1995 (2000). Using a time-series approach, a 0.5 ppm increase in same-

8   day 24-h avg CO concentration was associated with a 1.25% increase in CHF hospital admissions among

9   people aged >30 years. When the analyses were stratified by seasons only summer showed a significant

10   increase (3.7%); however, the study did not report the results for the other seasons.

11   A time-series study in Denver, Colorado, investigated daily admissions for various CVDs among

12   older adults (>65 years) across 11 hospitals (Koken et al., 2003). Single-day lags 0 to 4 were examined

13   and an increase of 0.5 ppm in 24-h avg CO concentration for lag 3 was associated with an 18%

14   (95% CI: 0.2-39.3) increase in risk of hospitalization for CHF.

15   As stated earlier, a study was conducted in Atlanta, GA, where over 4 million ED visits from

16   31 hospitals for the period 1993 to 2000 were analyzed (Metzger et al., 2004a). A time-series design was

17   used and a 3-day moving average over single-day lags 0-2 as the a priori lag structure was analyzed.

18   Results showed that 1-h max CO concentration was not associated with an increase in ED visits for CHF

19   (RR: 1.010 [95% CI: 0.988-1.032] per 1 ppm increase). When the analyses examined the same CVDs

20   among those with and without specific secondary conditions (e.g., co-morbidity) 1-h max CO

21   concentration was associated with an increase in ED visits for CHF only among those with COPD (OR:

22   1.058 [95% CI: 1.003-1.115] per 1 ppm increase) (Peel et al., 2007).

23   In Kaohsiung city, Taiwan, a study analyzed 13,475 admissions for CHF across 63 hosptials for the

24   period 1996 through 2004 (Lee et al., 2007a). A 0.5 ppm increase in 24-h avg CO concentration averaged

25   over lag days 0-2 was positively associated with CHF hospital admissions on cool days (<25°C) (OR:

26   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-

27   1.55]). These results persisted in two-pollutant models that included PM_{10}, SO_2, O_3, and models with NO_2

28   only on warmer days, not with NO_2 on cooler days.

29   Figure 5-3 shows the effect estimates for associations between CO and daily admissions for HF

30   from selected studies. Table 5-9 summarizes the HF hospital admission studies that examined CO

31   exposures.

32   In summary, many of the studies that examined associations between ambient CO concentrations

33   and daily hospital admissions for CHF reported significant associations at lags of 0 to 3 days.
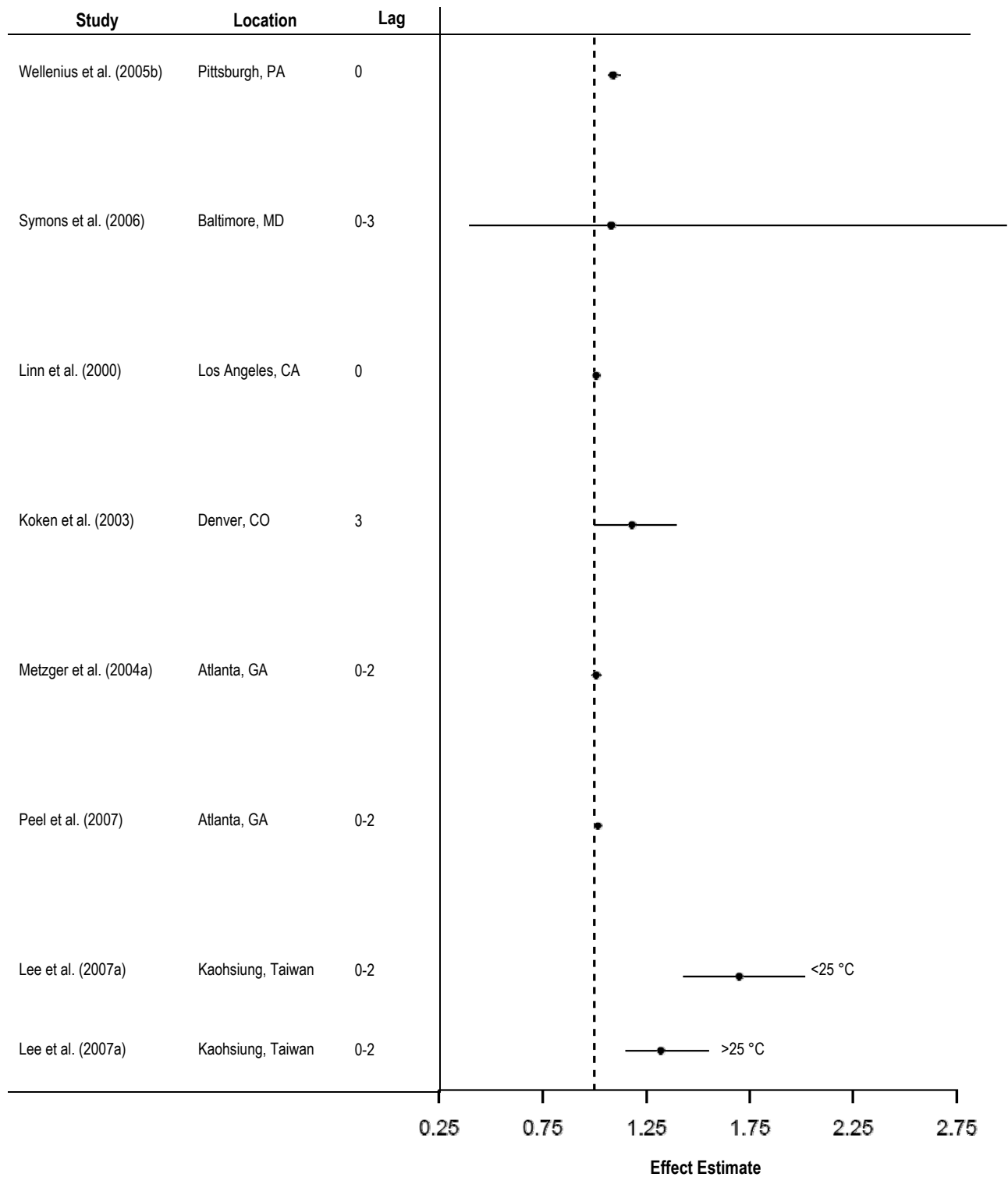
Figure 5.3. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for CHF. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-9.   Summary of HF hospital admission studies.

Study	Location	Endpoints Examined	Copollutants	Lags Examined	CO Levels (ppm)
STUDIES THAT FOCUSED SOLELY ON HF					
Wellenius et al. (2005b)	Pittsburgh, PA (1987-1999)	CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	Mean: 1.03 (24 h)
Symons et al. (2006)	Baltimore, MD (2002)	CHF	$PM_{2.5}$, NO_2, O_3	0,1,2,3	Mean: 0.4 (24 h)
Lee et al. (2007a)	Kaohsiung, Taiwan (1996-2004)	CHF	PM_{10}, NO_2, SO_2, O_3	0-2	Mean: 0.76 (24 h)
STUDIES THAT EXAMINED HF AMONG OTHER CVDS					
Linn et al. (2000)	Los Angeles, CA (1992-1995)	CHF, MI, All CVD, CA, OS	PM_{10}, NO_2, O_3	0	Mean: (24 h) Winter 1.7; Spring 1.0 Summer 1.2; Fall 2.1
Koken et al. (2003)	Denver, CO (1993-1997)	CHF, MI, CAth, PHD, CD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	Mean: 0.9 (24 h)
Metzger et al. (2004a)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean 1.5 (1 h)
Peel et al. (2007)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean 1.5 (1 h)

*Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhthmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.

Cardiovascular Diseases

1   The following section reviews studies that have investigated the effect of CO on ED visits and
2   hospital admissions for all CVD outcomes (e.g., non-specific). Several of these studies also examined
3   specific CVDs and were briefly discussed in previous sections.

4   As discussed earlier, a study was conducted in Atlanta, GA where over 4 million ED visits from
5   31 hospitals for the period 1993 to 2000 were analyzed (SOPHIA). Several articles have been published
6   from this research with three examining cardiovascular admissions in relation to CO exposures. The first
7   of these used a time-series design and analyzed a 3-day moving average over single-day lags 0-2 as the a
8   priori lag structure (Metzger et al., 2004a). Results showed that a 1 ppm increase in 1-h max CO
9   concentration was associated with an increase in daily ED visits for all CVDs (RR: 1.017
10   [95% CI: 1.008-1.027]). This persisted in two-pollutant models that included NO_2 and $PM_{2.5}$.
11   The second of these publications examined the association of ambient air pollution levels and
12   cardiovascular morbidity in visits with and without specific secondary conditions (Peel et al., 2007).
13   Within a time-stratified case-crossover design, a 3-day moving average over single-day lags 0-2 was used
14   as the a priori lag structure. Results from the case-crossover analyses on all cardiovascular and peripheral
15   vascular and cerebrovascular disease were similar to the time-series results presented earlier. Results from
16   the various co-morbidity analyses are presented in Table 5-10. Similar to the results from the earlier
17   publication, CO was mostly associated with peripheral vascular and cerebrovascular disease (PVCD)
18   among those with and without the co-morbidities, except among those with CHF. Overall, there is limited,
19   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	Dysryhthmias	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)	-
DYSRYHTHMIAS				
- 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: Peel et al. (2007)

1   The third study utilizing the SOPHIA data extended the time period to include 1993 through 2004

2   (Tolbert et al., 2007) and focused on two large outcome groups: a respiratory diseases group and a

3   cardiovascular diseases group. The combined cardiovascular case group included the following groups of

4   primary ICD-9 diagnostic codes: IHD (410-414), cardiac dysrhythmias (427), CHF (428), and peripheral

5   vascular and cerebrovascular disease (433-437, 440, 443-445, 451-453). Results showed that a 1 ppm

6   increase in 1-h max CO concentration was associated with an increase in daily ED visits for all CVDs

7   (RR: 1.016 [95% CI: 1.008-1.024]). CO was the strongest predictor of CVD effects in models with two-

8   pollutant combinations of NO_2, CO and TC, as well as in a model including all three pollutants.

9   Earlier research conducted in Los Angeles, CA, showed that a 0.5 ppm increase in same-day 24-h

10   avg CO concentration was associated with a 1.6% increase in CVD hospital admissions among people

11   aged >30 years (2000). When the analyses were stratified by season the significant CO effect was

12   strongest during winter (1.9% increase) followed by summer (1.8%) and fall (1.4%) with no effect in

13   spring.

14   In contrast to other North American studies, a study in Spokane, WA, did not find an association

15   between CO (lags of 1 to 3 days) and an increase in the number of daily cardiac hospital admissions

16   (quantitative results not reported) (Slaughter et al., 2005). Similarly, a time-series study in Windsor,

17   Ontario, did not find an association between ambient CO and daily hospital admissions for CVDs

18   (defined as HF, IHD, or dysrhythmias) (Fung et al., 2005). A total of 11,632 cardiac admissions were

1   analyzed for the period of 1995 to 2000. The lag periods analyzed in this study were lag 0 (same-day), a

2   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

3   mean percent change in daily admissions for the <65 age group (lag 0) was -2.6 (95% CI: -6.2 to 3.3); and

4   for the 65+ age group, 0.4 (95% CI: -1.9 to 2.7). The authors reported moderate to low correlations with

5   NO_2 (r = 0.38), PM_{10} (r = 0.21) and SO_2 (r = 0.16).

6   Two case-crossover studies in Taiwan reported an association between ambient CO and hospital

7   admissions for CVDs. In Taipei, a total of 74,509 CVD admissions from 47 hospitals for the period of

8   1997-2001 were analyzed (Chang et al., 2005). An increase of 0.5 ppm in 24-h avg CO concentration

9   (average over lags 0-2) during warmer periods ($\geq 20°C$) was associated with an increase in daily hospital

10   admissions (OR: 1.09 [95% CI: 1.065-1.121) but not cooler periods (<20°C) (OR: 0.98

11   [95% CI: 0.93-1.004]). These results persisted after controlling for PM_{10}, SO_2, or O_3 in two-pollutant

12   models. An identical study in Kaohsiung analyzed 29,661 CVD admissions for the period 1997-2000

13   (Yang et al., 2004b). Results showed that a 0.5 ppm increase in 24-h avg CO concentration was associated

14   with an increase in CVD hospital admissions during both the warmer periods (OR: 1.50

15   [95% CI: 1.38-1.63) and cooler periods (OR: 1.89 [95% CI: 1.69-2.12]).

16   Similarly, two Australian studies also reported associations between ambient CO concentrations

17   and increased hospital admissions among older adults. The first of these studies analyzed data from five

18   of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand

19   cities (Auckland, Christchurch) for the period 1998-2001 (Barnett et al., 2006). The combined estimates

20   showed that an increase of 0.75 ppm in the average 8-h max CO concentration over the current and

21   previous day (lag 0-1) was associated with a 1.8% (95% CI: 0.7-2.8) increase in all CVD admissions

22   among those aged 65+ years. Among those aged 15-64 years there was a smaller increase in CVD

23   admissions (1.0% [95% CI: 0.2-1.7]). The second of the Australian studies examined ED visits for CVDs

24   in older adults (65+ years) in Sydney for the period 1997 to 2001 (Jalaludin et al., 2006). A 0.75 ppm

25   increase in 8-h max CO concentration for single-day lags 0 and 1 was associated with increases in

26   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

27   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

28   of approximately 3% in CVD ED visits during the cool (May-October) period, but not the warm period

29   (November-April).

30   Very few studies investigating the association between CO and cardiovascular hospital admissions

31   have been conducted in European cities. Ballester et al. (2001) analyzed emergency hospital admissions

32   in Valencia, Spain for the period 1994 to 1996. The mean daily number of CVD admissions was 7 and

33   when using a time-series approach there was no association between CO and admissions for all CVDs

34   (RR: 1.009 [95% CI: 0.99-1.016] per 1 ppm increase in 1-h max CO concentration), heart diseases (RR:

35   1.010 [95% CI: 0.993-1.028] per 1 ppm increase), and cerebrovascular diseases (RR: 0.985

36   [95% CI: 0.959-1.012] per 1 ppm increase). When the analyses were stratified by hot and cold seasons,

1   only CO concentrations during the hot season were associated with an increase in all cardiovascular

2   admissions (RR: 1.033 [95% CI: 1.006-1.064] per 1 ppm increase), heart disease admissions (RR: 1.033

3   [95% CI: 1.000-1.067] per 1 ppm increase), and cerebrovascular admissions (RR: 1.074

4   [95% CI: 1.007-1.113] per 1 ppm increase).

5   Ballester et al. (2006) extended this research to include data from 14 Spanish cities for the period

6   of 1995 to 1999. An average exposure period over lags 0-1 was analyzed and for the combined estimates

7   a 0.75 ppm increase in 8-h max CO concentration was associated with a 1.77% (95% CI: 0.56-2.99)

8   increase in all cardiovascular emergency hospital admissions and a larger increase of 3.57%

9   (95% CI: 1.12-6.08) for heart disease admissions. These results persisted in two-pollutant models that

10   included NO_2, O_3 and SO_2.

11   Table 5.11 summarizes the non-specific CVD hospital admission studies that examined CO

12   exposures. Figure 5-4 shows the effect estimates associated with daily admissions for non-specific CVD

13   hospital admissions from selected studies.

14   In summary, many of the studies that examined associations between ambient CO concentrations

15   and ED visits and daily hospital admissions for CVD reported significant associations at short (0-1 day)

16   lags. Among studies that conducted stratified analyses, there were slightly stronger effects among older

17   adults and possibly during warmer periods.

Study	Location	Lag	
Tolbert et al. (2007)*	Atlanta, GA	0-2	
Linn et al. (2000)	Los Angeles, CA	0	All year
Linn et al. (2000)	Los Angeles, CA	0	Spring
Linn et al. (2000)	Los Angeles, CA	0	Summer
Linn et al. (2000)	Los Angeles, CA	0	Fall
Linn et al. (2000)	Los Angeles, CA	0	Winter
Fung et al. (2005)	Windsor, Canada	0-2	<65 years
Fung et al. (2005)	Windsor, Canada	0-2	65+ years
Chang et al. (2005)	Taipei, Taiwan	0-2	> 20°C Temp
Chang et al. (2005)	Taipei, Taiwan	0-2	< 20°C Temp
Yang et al. (2004a)	Kaohsiung, Taiwan	0-2	< 20°C Temp
Yang et al. (2004a)	Kaohsiung, Taiwan	0-2	> 20°C Temp
Barnett et al. (2006)	Australia, New Zealand	0-1	15-64 years
Barnett et al. (2006)	Australia, New Zealand	0-1	65+ years
Jalaludin et al. (2006)	Sydney, Australia	0-1	65+ years
Ballester et al. (2006)	Multi-city, Spain	0-1	

*Represents the results reported by Metzger et al. (2004b) and Peel et al. (2007)

Figure 5-4. **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 non-specific CVD hospital admission studies.

Study	Location	CVD Codes	Copollutants	Lags Examined	CO Levels (ppm)
Metzger et al. (2004a)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean: 1.5 (1 h)
Peel et al. (2007)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean 1.5 (1 h)
Tolbert et al. (2007)	Atlanta, GA (1993-2004)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	Mean 1.6 (1 h)
Linn et al. (2000)	Los Angeles, CA (1992-1995)	All CVD	PM_{10}, NO_2, O_3	0	Mean: (24 h) Winter 1.7; Spring 1.0; Summer 1.2; Fall 2.1
Slaughter et al. (2005)	Spokane, WA (1995-2001)	All CVD (ICD9: 390-459)	PM_{10}, $PM_{2.5}$, CO	1,2,3	Mean: range across 5 monitors 0.42-1.82 (24 h)
Fung et al. (2005)	Windsor, Canada (1995-2000)	All CVD (HF, IHF, or Dysrhythmia)	PM_{10}, NO_2, SO_2, O_3	0, 0-1, 0-2	Mean: 1.3 (24 h)
Chang et al. (2005)	Taipei, Taiwan (1997-2001)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	Mean: 1.37 (24 h)
Yang et al. (2004b)	Kaohsiung, Taiwan (1997-2000)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	Mean: 0.79 (24 h)
Barnett et al. (2006)	Australia and New Zealand (1998-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, O_3	0-1	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006)	Sydney, Australia (1997-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	Mean: 0.82 (8h)
Ballester et al. (2001)[1]	Valencia, Spain (1994-1996)	All CVD (ICD9: 390-459)	BS, NO_2, SO_2, O_3	1,2,3,4,5	Mean: 0.54 (24 h)
Ballester et al. (2006)[1]	Multi-city, Spain (1995-1999)	All CVD (ICD9: 390-459)	BS, PM_{10}, TSP, NO_2, SO_2, O_3	0-1	Mean: range across 14 cities 0.12-0.24 (8h)

[1] 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 tempterature.

1   Figure 5-5 summarizes the effects of CO concentration on ED visits and hospital admissions for all
2   CVD outcomes other than stroke from studies that presented the results from two-pollutant models.
3   Generally, the CO effect estimates from these studies are robust to the inclusion of copollutants, including
4   PM_{10}, $PM_{2.5}$, NO_2, SO_2, and O_3. In all but one instance (Lee et al., 2007a) (<25°C adjusted for NO_2) when
5   the single pollutant effect estimate was positive for CO, it remained positive after the addition of any of
6   the copollutants investigated.
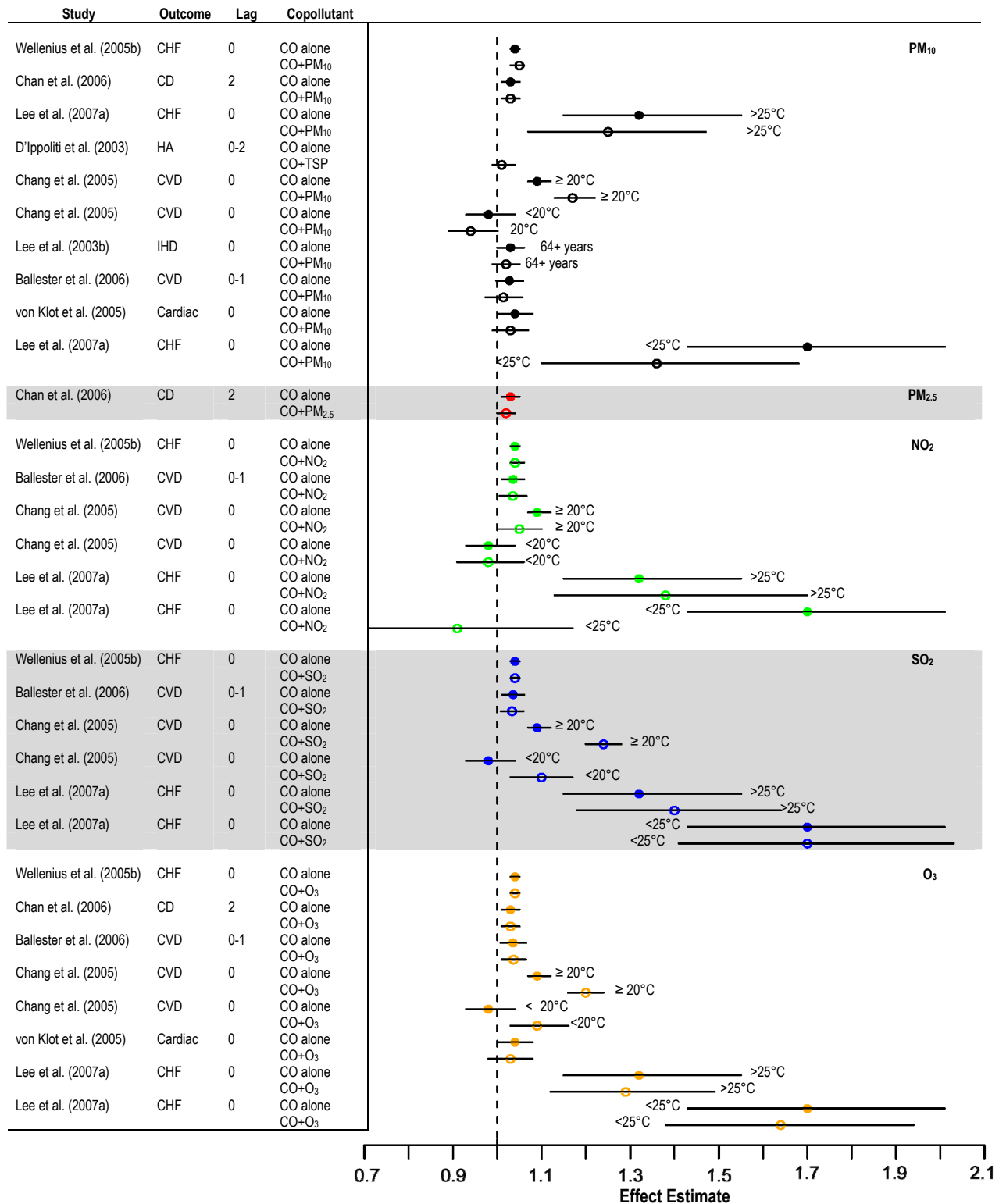
Figure 5-5. Effect estimates from studies of ED visits and hospital admissions for CVD outcomes other than stroke from single pollutant (CO only, closed circles) and copollutant (CO plus PM, NO₂, SO₂ and O₃, open circles) models. Effect estimates are standardized to 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO levels, and 0.5 ppm for 24-h avg CO concentrations.

5.2.1.2. Epidemiologic Studies with Long-Term Exposure

1   Only two studies examined CVD outcomes in association with long-term exposure to CO.
2 Rosenlund et al. (2006) investigated long-term exposure (30 years) to urban air pollution and the risk of
3 MI in Sweden. The study included 2,246 cases and 3,206 controls aged between 45 to 70 years and
4 residing in Stockholm County during 1992 to 1993. A detailed postal questionnaire was completed by
5 4067 subjects and all addresses inhabited during more than 2 years since 1960 were geocoded. The
6 exposures were then derived from dispersion calculations based on emissions data for each decade since
7 1960. These calculations were estimates of annual mean levels of traffic-generated NO_X, NO_2, CO, PM_{10},
8 and $PM_{2.5}$, with the addition of SO_2 from heating sources. The analyses were stratified by all cases,
9 nonfatal cases, fatal cases, in-hospital death, and out-of-hospital death. Based on a 30 year avg exposure
10 all pollutants were not associated with overall MI incidence. However, increased CO was associated with
11 out-of-hospital death from MI (OR: 1.81 [95% CI: 1.02-3.23] per 0.5 ppm increase in 30-year avg CO
12 concentration). Similar results were reported for NO_2. The correlation between the 30-year NO_2 and CO
13 exposures was reasonably strong (r = 0.74) and multipollutant models with both these pollutants included
14 (NO_2, CO) were not examined. No other pollutants were significantly associated with all other MI
15 outcomes.
16   A small-area ecologic study analyzed mortality and hospital admissions for stroke across 1,030
17 census districts in Sheffield, U.K. (Maheswaran et al., 2005b). Stroke counts within each census district
18 were linked to modeled air pollution data which was then grouped into quintiles of exposure. For stroke
19 hospital admissions, when the analyses were adjusted for only sex and age demographics there was an
20 exposure-response pattern exhibited across the quintiles of CO exposure with all levels reaching
21 significance (RR: 1.37 [95% CI: 1.24-1.52] for the highest exposure group compared to the lowest
22 group). However, this result did not persist when also adjusting for a deprivation index and smoking rates
23 across the districts (RR: 1.11 [95% CI: 0.99-1.25]).

5.2.1.3. Summary of Epidemiologic Studies of Exposure to CO and Cardiovascular Effects

24   A substantial number of epidemiologic studies have examined the potential association between
25 exposure to CO and various physiological cardiac endpoints or biomarkers. Overall, despite some mixed
26 results reported among panel and retrospective cohort studies, there was evidence that exposure to CO has
27 an effect on HR, various HRV parameters, and blood markers of coagulation and inflammation.
28 Conversely, based on results from panel studies there was little evidence of a link between CO and
29 cardiac arrhythmia, cardiac arrest, the occurrence of myocardial infarction, and increased BP.

1   Studies of ED visits and hospital admissions provide evidence that CO is associated with various

2   forms of CVD with lag periods ranging from 0 to 3 days. There is little evidence that ambient CO is

3   associated with an increase in hospital admissions for ischemic stroke. Studies of hospital admissions and

4   ED visits for IHD and CHF provide the strongest evidence of ambient CO being associated with adverse

5   CVD outcomes. It is difficult to determine from this group of studies the extent to which CO is

6   independently associated with CVD outcomes or if CO is a marker for the effects of another traffic-

7   related pollutant or mix of pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of

8   combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road

9   locations. Although this complicates the efforts to disentangle specific CO-related health effects, the

10   evidence indicates that CO associations generally remain robust in copollutant models, are coherent with

11   the effects demonstrated by controlled human exposure and animal toxicological studies, and supports a

12   direct effect of short-term CO exposure on CVD morbidity at ambient concentrations below the current

13   NAAQS level. Such direct effects are plausible considering that long-term, low concentration CO

14   exposure (See Section 4.2.3) could result in a COHB level approaching those used in controlled human

15   exposure studies (See Section 5.2.2).

5.2.2. Controlled Human Exposure Studies

16   Controlled human exposure studies provide valuable information related to the health effects of

17   exposure to air pollutants following short term exposures. These types of experiments are often referred to

18   as human clinical studies and are conducted in a laboratory setting under carefully regulated exposure

19   concentrations, environmental conditions, and subject activity levels. Human clinical studies are typically

20   conducted using a randomized crossover study design with subjects exposed to both the pollutant(s) of

21   interest and a clean air control. Results of controlled human exposure studies can be used to provide

22   coherence with the evidence from epidemiologic studies by expanding the understanding of potential

23   mechanisms for the observed health outcomes. However, they may also provide information that can be

24   used directly in quantitatively characterizing the exposure concentration-health response relationships at

25   ambient or near-ambient concentrations. Human clinical studies are limited by a number of factors

26   including a small sample size and relatively short exposure time. In addition, although health-

27   compromised individuals have been included in human clinical studies, all subjects participating must be

28   relatively healthy and do not represent the most sensitive individuals in the population.

29   Several human clinical studies cited in the 2000 CO AQCD observed changes in measures of

30   cardiovascular function among individuals with CAD following short term exposures to CO. In a multi-

31   laboratory study of men with stable angina, Allred et al. (1989, 1991) evaluated the effect of CO exposure

32   on exercise-induced angina and ST-segment changes indicative of myocardial ischemia. Relative to clean

1   air exposure (COHb ≈ 0.6%), exposures to CO resulting in COHb concentrations of 2.4% and 4.7% were

2   shown to decrease the time required to induce ST-segment changes by 5.1% (p = 0.02) and 12.1%

3   (p <0.001), respectively. These changes were well correlated with the onset of exercise-induced angina. A

4   number of other studies involving individuals with stable angina have also demonstrated a CO-induced

5   decrease in time to onset of angina as well as reduction in duration of exercise at COHb concentrations

6   between 3 and 6% (Adams et al., 1988; Anderson et al., 1973) (Kleinman et al., 1989; Kleinman et al.,

7   1998). However, Sheps et al. (1987) observed no change in time to onset of angina or maximal exercise

8   time following a 1-h exposure to 100 ppm CO (targeted COHb of 4%) among a group of 30 patients with

9   CAD. In a subsequent study conducted by the same laboratory, a significant increase in number of

10   ventricular arrhythmias during exercise was observed relative to room air among individuals with CAD

11   following a 1-h exposure to 200 ppm CO (targeted COHb of 6%), but not following a 1-h exposure to

12   100 ppm CO (targeted COHb of 4%) (Sheps et al., 1990). It should be noted that although the subjects

13   evaluated in the studies described above are not necessarily representative of the most sensitive

14   population, the level of disease in these individuals was relatively severe, with the majority either having

15   a history of MI or having ≥ 70% occlusion of one or more of the coronary arteries.

16   The 2000 CO AQCD presented very little evidence of CO-induced changes in cardiovascular

17   function in healthy adults. Davies and Smith (1980) exposed healthy young adults continuously for 7 days

18   to CO concentrations of 0, 15, or 50 ppm. In this study, a marked ST-segment depression was

19   demonstrated in only 1 out of 16 subjects following exposure to 15 ppm CO (2.4% COHb) or 50 ppm CO

20   (7.2% COHb). Since the publication of the 2000 CO AQCD, no new human clinical studies have been

21   published involving controlled CO exposures among subjects with CAD. However, a number of new

22   studies have evaluated changes in various measures of cardiovascular and systemic responses following

23   controlled exposures to CO in healthy adults. Adir et al. (1999) exposed 15 young healthy adult males to

24   room air or CO for approximately 4 min, using a CO exposure concentration which had been shown to

25   produce the targeted COHb level of 4-6%. Following each exposure, subjects performed an exercise

26   treadmill test at their maximal capacity. Exposure to CO was not observed to cause arrhythmias,

27   ST-segment changes, or changes in myocardial perfusion (thallium scintigraphy) during post-exposure

28   exercise. However, CO was demonstrated to decrease the post-exposure duration of exercise by

29   approximately 10% (p = 0.0012). In addition, the authors reported significant CO-induced decreases in

30   metabolic equivalent units (p <0.001), which is a relative measure of O_2 consumption. These results

31   support the findings of several studies cited in the 2000 CO AQCD which observed decreases in exercise

32   duration and maximal aerobic capacity among healthy adults at COHb levels ≥ 3% (Drinkwater et al.,

33   1974; Ekblom and Huot, 1972; Horvath et al., 1975; Raven et al., 1974). While these decreases in

34   exercise duration were relatively small and only likely to be noticed by competing athletes, the findings

35   are nonetheless important in providing coherence with the observed effects of CO on exercise-induced

36   myocardial ischemia among patients with CAD.

1   Kizakevich et al. (2000) evaluated the cardiovascular effects of increasing CO concentration in

2   healthy adults engaged in upper and lower body exercise. Subjects were initially exposed for 4-6 min to

3   CO concentrations between 1,000 and 3,000 ppm, followed by continued exposure to 27, 55, 83, and

4   100 ppm to maintain COHb levels of 5, 10, 15, and 20%, respectively. Relative to room air control, CO

5   exposure was not observed to cause ST-segment changes or affect cardiac rhythm at any concentration

6   during either upper or lower body exercise. Compensation mechanisms for reduced O_2 carrying capacity

7   during CO exposure were demonstrated, with statistically significant increases in heart rate occurring at

8   COHb levels ≥ 5%, and statistically significant increases in cardiac output and cardiac contractility

9   observed at COHb levels ≥ 10%. In a human clinical study designed to evaluate the contribution of CO to

10   cardiovascular morbidity associated with cigarette smoking, Zevin et al. (2001) exposed 12 healthy male

11   smokers for 7 consecutive days to clean air, CO, or cigarette smoke, with each subject serving as his own

12   control. The COHb levels were similar between the exposures to cigarette smoke and CO, with average

13   concentrations of 6% and 5%, respectively. Cigarette smoke, but not CO, was observed to significantly

14   increase plasma levels of CRP and plasma platelet factor 4 relative to the air control arm of the study.

15   Neither cigarette smoke nor CO was shown to affect BP. Hanada et al. (2003) observed an increase in leg

16   muscle sympathetic nerve activity (MSNA) following controlled exposures to CO (COHb ≈20%) under

17   normoxic or hyperoxic conditions. Although an increase in the magnitude of sympathetic activation is

18   typically associated with regional vasoconstriction, no CO-induced changes in femoral venous blood flow

19   were observed in this study. These findings are in agreement with those of Hausberg et al. (1997) who

20   observed no change in forearm blood flow or BP in a study of 10 healthy men and women following a

21   controlled exposure to CO (COHb ≈ 8%). Interestingly, one recent study did observe an increase in retinal

22   blood flow, retinal vessel diameter, and choroidal blood flow following controlled exposures to CO at a

23   concentration of 500 ppm (Resch et al., 2005). This protocol resulted in COHb concentrations of 5.6%

24   and 9.4% following exposures of 30 and 60 min, respectively, with statistically significant increases in

25   retinal and choroidal blood flow observed at both time points relative to synthetic air control. This

26   CO-induced change in ocular hemodynamics may have been due to local tissue hypoxia; however, the

27   clinical significance of this finding is unclear. Exposures to CO have also been shown to affect skeletal

28   muscle function, with one recent human clinical study reporting a decrease in muscle fatigue resistance in

29   healthy adult males using both voluntary and electrically-induced contraction protocols following

30   controlled exposures to CO resulting in an average COHb level of 6% (Morse et al., 2008).

31   In summary, controlled human exposures to CO among individuals with CAD have been shown to

32   consistently increase markers of myocardial ischemia at COHb levels between 3 and 6%, with one study

33   reporting similar effects following CO exposures resulting in COHb concentrations of 2.4%. No such

34   effects have been observed in healthy adults following controlled exposures to CO. Although some

35   studies have reported CO-induced hemodynamic changes among healthy adults at COHb concentrations

36   of as low as 5%, this effect has not been consistent across studies.

5.2.3. Toxicological Studies

1   While novel toxicological research on environmental levels of CO was limited in the 2000 CO

2   AQCD, several sections reported potential relationships between CO exposure and cardiovascular effects.

3   Conflicting experimental data relating to the role of CO in promoting atherosclerotic vessel disease was

4   discussed. While some animal studies have linked chronic CO exposure with atherosclerosis development

5   resulting from increased fatty streaking and cellular lipid loading (Davies et al., 1976; Thomsen, 1974;

6   Turner et al., 1979), other studies have failed to see this association (Penn et al., 1992; Stupfel and

7   Bouley, 1970). Ventricular hypertrophy has also been shown after chronic CO exposure (Penney et al.,

8   1984; Penney et al., 1988).

9   The following sections describe recent studies dealing with toxicity of relatively low levels of CO.

10   There has been little new research with the overt purpose of examining environmentally-relevant levels of

11   CO. For the most part, studies were designed to mimic exposures related to cigarette smoke, either side-

12   stream or mainstream, accidental CO poisoning, or for the purposes of therapeutic application. Thus, few

13   studies examined levels of CO within the current 1 h (35 ppm) or 8 h (9 ppm) NAAQS levels, and fewer

14   still examined concentration response curves to delineate no effects levels. However, it is apparent that

15   CO, at low to moderate levels (35-250 ppm), has pathophysiological effects on the cardiovascular system

16   and on relatively ubiquitous cellular pathways.

17   CO exposure at environmentally-relevant levels is unlikely to overwhelm normal physiology in a

18   healthy cell; however, susceptibility may be rendered by disease or early development. A common theme

19   appears to be the vulnerability of vascular cells, especially the endothelium, which could be considered

20   the first organ of contact once taken up into the circulation. While relatively little research has been

21   conducted since the 2000 CO AQCD, several key studies conducted at near-environmental CO levels

22   provide important clues to the potential public health implications of ambient CO exposure.

5.2.3.1. Endothelial Dysfunction

23   While the preferential binding to heme and effective displacement of O_2 by CO has been well

24   established for over a century, new information from various fields of study are beginning to elucidate

25   non-hypoxic mechanisms that may lead to cardiovascular abnormalities associated with CO exposure.

26   Research by Thom, Ischiropoulos, and colleagues (Ischiropoulos et al., 1996; Thom et al., 1994; Thom

27   and Ischiropoulos, 1997; Thom et al., 1997; Thom et al., 1999a; Thom et al., 1999b; Thom et al., 2000;

28   Thom et al., 2006) has focused on CO-mediated displacement of $NO^{\bullet}$ from heme-binding sites. Some of

29   this work demonstrates a specific pathway by which severe CO poisoning can lead to the release $NO^{\bullet}$

30   from platelets with subsequent neutrophil activation and vascular injury (Ischiropoulos et al., 1996; Thom

31   et al., 2006). The steps include (1) peroxynitrite generation from the reaction of $NO^{\bullet}$ from platelets with

1   neutrophil-derived superoxide followed by (2) stimulation of intravascular neutrophil degranulation that

2   can result in (3) myeloperoxidase deposition along the vascular lining. Products from myeloperoxidase-

3   mediated reactions can cause endothelial cell activation (Thom et al., 2006) and can lead to endothelial

4   dysfunction. The concentrations used in these studies are greatly in excess of the NAAQS levels, but

5   certainly within the range of accidental or occupational exposures. Research by these same investigators

6   at more environmentally-relevant CO levels was partially reviewed in the 2000 CO AQCD. The release of

7   free $NO^\bullet$ was noted in isolated rat platelets exposed to 10-20 ppm CO (Thom and Ischiropoulos, 1997).

8   Increased nitrotyrosine content of the aorta was observed in rats exposed to 50 ppm CO for 1 h (1999a;

9   Thom et al., 1999b). Furthermore in this same study, a 1-h exposure to 100 ppm CO led to albumin efflux

10   from skeletal muscle microvasculature at 3 h and leukocyte sequestration in the aorta at 18 h. LDL

11   oxidation was also reported. These effects were dependent on NOS but not on neutrophils or platelets. A

12   second study demonstrated NO-dependent effects of 50-100 ppm CO in lungs and is described in Section

13   5.5.4 (Thom et al., 1999b). Studies in cultured endothelial cells were also conducted using buffer

14   saturated with 10-100 ppm CO (Thom et al., 1997). These experiments were designed to mimic

15   conditions where blood COHb levels were between 3.8 and 28% resulting in exposure of endothelial cells

16   to 11-110 nM CO. CO-stimulated release of $NO^\bullet$ from endothelial cells along with peroxynitrite

17   formation and delayed cell death was observed at CO concentrations of 22 nM and higher (Thom et al.,

18   1997). A more recent study demonstrated adaptive responses in endothelial cells exposed to this same

19   range of CO concentrations (Thom et al., 2000). Specifically, 1-h exposure to 11 nM CO resulted in

20   MnSOD and HO-1 induction and resistance to the apoptotic effects of 110 nM CO. These protective

21   effects of CO were mediated by $NO^\bullet$, as demonstrated using an inhibitor of NOS and a scavenger of

22   peroxynitrite. Collectively, these experiments demonstrated altered oxidative stress, the initiation of

23   inflammation, increased microvascular permeability and altered cell signaling in animals and isolated

24   cells following exposure to 10-100 ppm CO.

25   CO is an endogenous regulator of vasomotor tone through vasodilatory effects mediated by

26   activation of soluble guanylate cyclase and activation of large conductance Ca^{2+} activated K^+ channels.

27   However, CO does not cause vasodilation in every vascular bed. For example, 5, 100, 500 and 2,500 ppm

28   CO administered by inhalation to near-term fetal lambs did not induce pulmonary vasodilation and the

29   HO inhibitor zinc protoporphyrin IX failed to affect baseline vascular tone (Grover et al., 2000). In some

30   cases CO promotes vasoconstriction, which is thought to be mediated by inhibition of endothelial NOS

31   (Johnson et al., 2003; Thorup et al., 1999) or decreased $NO^\bullet$ bioavailability. An interesting series of

32   studies has also suggested that endogenous CO derived from HO-1 which is induced in a variety of

33   disease models (salt-sensitive forms of hypertension, metabolic syndrome in obese rats) is responsible for

34   skeletal muscle arterial endothelial dysfunction (Johnson et al., 2003, 2004; Teran et al., 2005). Additional

35   studies will be useful in determining whether environmentally-relevant concentrations of CO have

36   detrimental effect on pre-existing conditions such as hypertension, metabolic syndrome or pregnancy.

1   Several recent animal studies examined the vascular effects of controlled exposures to complex

2   combustion mixtures containing CO. Vascular dilatation was decreased following exposure to diesel (4 h

3   at 4 ppm) (Knuckles et al., 2008) and gasoline engine emissions (6 h/day x 1, 3, and 7 day at 80 ppm)

4   (Lund et al., 2009). Furthermore, evidence of vascular ROS following gasoline emissions has been shown

5   in certain animal models (6 h/day x 50 day at 8-80 ppm) (Lund et al., 2007). While none of these studies

6   examined the potential role of CO, alone or in combination, it is clearly a common factor in the various

7   combustion atmospheres, and future work will be needed to reveal its importance on vascular health.

5.2.3.2. Cardiac Remodeling Effects

8   Cardiomyopathy, or abnormal growth of the cardiac muscle, can manifest in different ways,

9   depending on the nature of the insult. The adverse effects of cardiac hypertrophy are due to reduction of

10   ventricular chamber volume and a diminishing efficiency of the heart. Such concentric hypertrophy

11   typically occurs in response to chronic increases in load, as occurs with hypertension. Ischemia of the

12   cardiac tissue can also lead to cardiac remodeling and myopathy. During and after an acute infarction or

13   obstruction of major coronary vessels, downstream tissues can suffer severe regional ischemia that leads

14   to significant necrosis. Such regions will lose the ability to contract, and surrounding tissue will show

15   deficits in contractility. Decreased contractility is often a result of structural thinning of the ventricular

16   wall, as well as metabolic impairments. Chronic ischemia, such as may result from CAD, may similarly

17   impair cardiomyocyte function and cause decreased contractility and remodeling. However, ultimately

18   cardiomyopathies are of a complex origin involving mismanagement of fluid balance, abnormal hormonal

19   influences (epinephrine, angiotensin), and insufficient perfusion/nutrition. Assessing the role of

20   exogenous CO in altering pathways leading to cardiomyopathy is a relatively new endeavor and several

21   new findings are of great interest.

22   The heart is a known target for CO toxicity, potentially due to its high rate of O_2 consumption.

23   Direct effects of CO on the healthy heart have only been observed at relatively high concentrations. For

24   example, a recent study by Sorhaug et al. (2006) demonstrated cardiac hypertrophy in rats exposed for 72

25   weeks to 200 ppm CO. COHb levels were reported to be 14.7%. Neither structural signs of hypertension

26   in the pulmonary arteries or atherosclerotic lesions in the systemic arteries were observed. Cardiac

27   hypertrophy was also demonstrated in rats exposed to 100-200 ppm CO for 1-2 weeks (Loennechen et al.,

28   1999). This response was accompanied by an increase in endothelin-1 expression. COHb levels were

29   reported to be 12-23% in this study.

30   Direct effects of CO on the healthy heart have also been demonstrated following short-term

31   exposures. In a study by Favory et al. (2006b), rats were exposed to 90 min of 250 ppm CO, which led to

32   peak COHb values of roughly 11%; recovery of 96 h was needed for COHb levels to return to baseline.

33   The authors noted that within the first 24 hours of recovery, while COHb values decreased from 11% to

1   5%, the coronary vascular perfusion pressure and the left ventricular developed pressure were

2   significantly increased compared to baseline. Concomitantly, the ratio of cGMP to cAMP decreased and

3   the sensitivity of the coronary vascular bed to both acetylcholine and a NO$^\bullet$ donor were reduced by CO

4   exposure. The authors concluded that the discordant alterations in contractility (increased) and perfusion

5   (decreased) may place the heart at risk of O_2 limitations following this exposure to CO.

6   Several studies examined the impact of lower levels (50 ppm) on pre-existing or concurrent cardiac

7   pathologies. In one such study, CO exacerbated the effects of a hypoxia-based model of right ventricular

8   remodeling and failure (Gautier et al., 2007). In controlled laboratory settings, chronic hypobaric hypoxia

9   (HH) caused right ventricular hypertrophy as a result of pulmonary arterial vasoconstriction and increased

10   pulmonary resistance. Using such a model (Wistar rats exposed for 3 weeks to hypoxia), CO (50 ppm

11   during the last week of hypoxia, continuous) only increased COHb from 0.5% to 2.4% in the hypoxia

12   model, yet had significant effects on blocking compensatory functional responses to hypoxia, such as

13   increased fractional shortening and contractility. Also, while right ventricular weight was increased by

14   hypoxia alone, significant pathology related to necrosis was observed in the hypoxia + CO-exposed rats.

15   The reduced coronary perfusion of the right ventricle in hypoxia + CO-exposed rats may help explain the

16   histopathological findings. The authors cited previous work demonstrating that exogenous CO can inhibit

17   NOS (Thorup et al., 1999), which is essential for coronary dilation and angiogenesis. Thus, this study

18   provided evidence that exogenous CO may interrupt or downregulate pathways that endogenous CO may

19   activate.

20   In two studies by Melin et al. (2002; 2005), Dark Agouti rats were exposed for 10 weeks to either

21   HH, 50 ppm CO or HH plus 50 ppm CO. CO exposure amplified the right ventricular cardiac hypertrophy

22   and decreased the right ventricular diastolic function which occurred in response to HH. In addition, the

23   combined exposure led to effects on left ventricular morphology and function which were not seen with

24   either exposure alone. Changes in HRV were also reported. Results from both of these studies combined

25   with results of Gautier and colleagues (2007) indicated that CO may interfere with normal homeostatic

26   responses to hypoxia. This could occur by blocking HIF-1α-responsive elements (vascular endothelial

27   growth factor, erythropoietin) or other cell signaling pathways.

28   In a similar study, Carraway et al. (2002) exposed rats to HH (380 torr) with or without co-

29   exposure to CO (50 ppm). These exposures were continuous for up to 21 days and focused on pulmonary

30   vascular remodeling. While the addition of CO to HH did not alter the thickness or diameter of vessels in

31   the lung, there was a significant increase in the number of small (<50 μm) diameter vessels compared to

32   control, HH only, and CO-only exposures. Despite the greater number of vessels, the overall pulmonary

33   vascular resistance was increased in the combined CO + hypoxic exposure, which the authors attributed

34   to enhancement of muscular arterioles and β-actin. Results of this study taken together with results from

35   the Gautier et al. (2007) and Melin studies (2002; 2005) suggested that the combined effect of low levels

36   of CO with hypoxia is an enhanced right ventricle workload and an exacerbated cardiomyopathy related

1 to pulmonary hypertension. The population at risk of primary pulmonary hypertension is low, but

2 secondary pulmonary hypertension is a frequent complication of COPD and certain forms of heart failure.

5.2.3.3. Electrocardiographic Effects

3   In two related studies, Wellenius et al. (2004; 2006b) examined the effect of CO on a rat model of

4 ischemia-related arrhythmia that was previously shown to produce significant results with exposures to

5 PM (Wellenius et al., 2002). ECG changes were observed during exposure to residual oil fly ash (ROFA)

6 particles in a rat model of MI. Thus, using an anesthetized model of post-infarction myocardial sensitivity,

7 Wellenius and colleagues tested the effects of 35 ppm CO (1-h exposure) on the induction of spontaneous

8 arrhythmias in Sprague Dawley rats (Wellenius et al., 2004). CO exposure caused a statistically

9 significant decrease (60.4%) in ventricular premature beat (VPB) frequency during the exposure period in

10 rats with a high number of pre-exposure VPB. No interaction was observed with co-exposure to carbon

11 concentrated particles, which independently reduced VPB frequency during the post-exposure period

12 when administered alone. In a follow-up publication, results from the analysis of supraventricular ectopic

13 beats (SVEB) were provided (Wellenius et al., 2006b). A decrease in the number of SVEB was observed

14 with CO (average concentration 37.9 ppm) compared to filtered air. While the authors concluded that CO

15 exposure did not increase risk of SVEB in this particular rodent model of coronary occlusion, the fact that

16 cardiac electrophysiological dynamics are significantly altered by short-term exposure to low level CO

17 may be of concern for other models of susceptibility.

5.2.3.4. Summary of Cardiovascular Toxicology

18   Recent studies demonstrated that short-term exposure to 50-100 ppm CO resulted in aortic injury

19 as measured by increased nitrotyrosine and the sequestration of activated leukocytes in healthy rats. In

20 addition, skeletal muscle microvascular permeability was increased. Short term-exposure to 35 ppm CO

21 altered cardiac electrophysiology in a rat model of myocardial ischemia. Furthermore short-term exposure

22 to 50 ppm CO exacerbated cardiac pathology and impaired function in animal models of hypertrophic

23 cardiomyopathy and/or pulmonary hypertension. Ventricular hypertrophy was observed in healthy rats in

24 response to chronic exposures of 100-200 ppm CO. These studies provide a strong basis for the

25 development of adverse health effects resulting from exposures to CO at environmentally-relevant

26 concentrations.

5.2.4. Summary of Cardiovascular Effects

1   The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb
2   levels relevant to the current NAAQS comes from a series of controlled human exposure studies among
3   individuals with CAD (see Section 5.2). These studies, described in the 1991 and 2000 CO AQCDs,
4   demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes
5   following CO exposures resulting in COHb levels of 3-6%, with one multicenter study reporting similar
6   effects at COHb levels as low as 2.4%. No human clinical studies have evaluated the effect of controlled
7   exposures to CO resulting in COHb levels lower than 2.4%. Human clinical studies published since the
8   2000 CO AQCD have reported no association between CO and ST-segment changes or arrhythmia;
9   however, none of these studies included individuals with diagnoses of heart disease.

10   While the exact physiological significance of the observed ST-segment changes among individuals
11   with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also
12   important to note that the individuals with CAD who participated in these controlled exposure studies
13   were not representative of the most sensitive individuals in the population. In fact, the most sensitive
14   individuals may respond to levels of COHb lower than 2.4%. Variability in activity patterns and severity
15   of disease among individuals with CAD is likely to influence the critical level of COHb which leads to
16   adverse cardiovascular effects.

17   The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also
18   vary between individuals. First of all, endogenous CO production varies as described in Section 4.5, but
19   generally results in less than 1% COHb. Secondly, nonambient exposures to CO, such as exposure to
20   ETS, can increase COHb above baseline levels. Ambient exposures will result in an additive increase in
21   COHb. Using mathematical modeling to predict changes in COHb in healthy inactive adults (Quantitative
22   Circulatory Physiology [QCP] model, Section 4.2.3), it can be estimated that exposure to 35 ppm CO for
23   1 h results in an increase of 0.6% COHb over baseline and exposure to 9 ppm CO for 8 h results in an
24   increase of 0.8% COHb over baseline. Furthermore, 24 h exposure to 3 ppm CO results in an increase of
25   0.4% COHb above baseline which can also be obtained following 1-h exposure to 30 CO ppm.
26   Consequently, exposure to CO at concentrations relevant to the NAAQS has the potential to increase
27   COHb to levels associated with adverse cardiovascular health effects in some individuals.

28   Findings of controlled human exposure studies are coherent with findings of recent epidemiologic
29   studies conducted since the 2000 CO AQCD, which observed associations between ambient CO
30   concentration and ED visits and hospital admissions for IHD, CHF and all-cause cardiovascular disease.
31   All but one of these epidemiologic studies were conducted in locations where the entire distribution of
32   CO concentrations were at or below the level of the current NAAQS, with mean 24-h avg concentrations
33   ranging from 0.5 ppm (Montreal, Canada) to 9.4 ppm (Tehran, Iran) (Table 5-7). A single study reported a
34   negative association between CO concentration and hospital admissions and ED visits for IHD among all

1   ages; all other associations were positive, with increases in hospital admissions and ED visits for IHD

2   between 0.2% and 19.8% per standardized increase in CO concentration (Figure 5-1). These recent

3   studies build upon the conclusions of the 2000 CO AQCD that short-term variations in ambient CO

4   concentrations are associated with daily hospital admissions for heart disease.

5   These health outcomes are consistent with a role for CO in limiting O_2 availability (i.e., hypoxic

6   mechanisms) in individuals with CAD. However, recent toxicological studies suggested that CO may also

7   act through non-hypoxic mechanisms by disrupting cellular signaling. Studies in healthy animals

8   demonstrated oxidative injury and inflammation in response to 50-100 ppm CO while studies in disease

9   models demonstrate effects on heart rhythm and exacerbation of cardiomyopathy and vascular remodeling

10 in response to 35-50 ppm CO. Furthermore, in utero exposure to 150 ppm CO alters postnatal

11 elecrophysiological maturation in rat cardiomyocytes. Further investigations will be useful in determining

12 the importance of non-hypoxic mechanisms following environmentally-relevant CO exposures. Taken

13 together, the evidence from epidemiologic, human clinical and toxicological studies is sufficient to

14 conclude that **a causal relationship is likely to exist between relevant short-term CO exposures and**

15 **cardiovascular morbidity.**

5.3. Central Nervous System Effects

5.3.1. Controlled Human Exposure Studies

16   The behavioral effects of controlled human exposures to CO have been examined by several

17 laboratories, and these studies were summarized in the 2000 CO AQCD. Briefly, decreases in visual

18 tracking as well as visual and auditory vigilance were observed following exposures to CO resulting in

19 COHb levels between 5% and 20% (Benignus et al., 1987; Fodor and Winneke, 1972; Horvath et al.,

20 1971; Putz et al., 1979). One study reported similar behavioral effects (time discrimination) among a

21 group of healthy volunteers with COHb levels <3% (Beard and Wertheim, 1967); however, subsequent

22 studies were unable to replicate these findings at such low exposure concentrations (Otto et al., 1979;

23 Stewart et al., 1973a). These outcomes represent a potentially important adverse effect of CO exposure

24 resulting in COHb levels $\geq$ 5%, although it is important to note that these findings have not been

25 consistent across studies. Similarly, some studies demonstrated decreases in reaction time as well as

26 decrements in cognitive function and fine motor skills following controlled exposures to CO; however,

27 these studies were not typically conducted using double-blind procedures, which may significantly affect

28 the outcome of behavioral studies (Benignus, 1993). It should be noted that all behavioral studies of

1   controlled CO exposure were conducted in normal, healthy adults. No new human clinical studies have

2   evaluated CNS or behavioral effects of exposure to CO.

5.3.2. Toxicological Studies

3   The evidence for toxicological effects of CO exposure in laboratory animal models comes from in

4   utero or perinatal exposure to relatively low levels of CO (25 to 750 ppm). Affected endpoints from this

5   early, developmental CO exposure include behavior, memory, learning, locomotor ability, peripheral

6   nervous system myelination, auditory decrements, and neurotransmitter changes. These data are

7   addressed in detail in the birth outcomes section of the ISA (Section 5.4.2).

5.3.3. Summary of Central Nervous System Effects

8   Exposure to high levels of CO has long been known to adversely affect CNS function, with

9   symptoms following acute CO poisoning including headache, dizziness, cognitive difficulties,

10   disorientation, and coma. However, the relationship between ambient levels of CO and neurological

11   function is less clear and has not been evaluated in epidemiologic studies. Studies of controlled human

12   exposures to CO discussed in the 2000 CO AQCD reported inconsistent neural and behavioral effects

13   following exposures resulting in COHb levels of 5-20%. No new human clinical studies have evaluated

14   central nervous system or behavioral effects of exposure to CO. At ambient-level exposures, healthy

15   adults may be protected against CO-induced neurological impairment owing to compensatory responses

16   including increased cardiac output and cerebral blood flow. However, these compensatory mechanisms

17   are likely impaired among certain potentially susceptible groups, including individuals with reduced

18   cardiovascular function.

19   Toxicological studies that were not discussed in the 2000 CO AQCD employed rodent models to

20   show that low level CO exposure during the in utero or perinatal period can adversely affect adult

21   outcomes including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory

22   system (discussed in Section 5.3). In utero CO exposure, including both intermittent and continuous

23   exposure, has been shown to impair multiple behavioral outcomes in offspring including active avoidance

24   behavior (150 ppm CO), non-spatial memory (75 and 150 ppm CO), spatial learning (endogenous CO

25   inhibition), homing behavior (150 ppm CO), locomotor movement (150 ppm CO), and negative geotaxis

26   (125 and 150 ppm). In two separate studies, in utero CO exposure (75 and 150 ppm) was associated with

27   significant myelination decrements without associated changes in motor activity in adult animals.

28   Multiple studies demonstrated that in utero CO exposure affected glutamatergic, cholinergic,

29   catecholaminergic, and dopaminergic neurotransmitter levels or transmission in exposed male rodents.

1   Possible or demonstrated adverse outcomes from the CO-mediated aberrant neurotransmitter levels or

2   transmission include respiratory dysfunction (200 ppm CO), impaired sexual behavior (150 ppm CO), and

3   an adverse response to hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal

4   CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent

5   changes into adulthood. This is manifested with atrophy of cochlear cells innervating the inner hair cells

6   (25 ppm CO), decreased immunostaining associated with impaired neuronal activation (12.5 ppm CO),

7   impaired myelination of auditory associated nerves (25 ppm CO), decreased energy production in the

8   sensory cell organ of the inner ear or the organ of corti (25 ppm CO), some of which is mechanistically

9   proposed to be mediated by ROS (25 ppm CO). Functional tests of the auditory system of neonatally, low

10 level CO-exposed rodents, using OAE testing (50 ppm) and amplitude measurements of the 8th cranial

11 nerve action potential (12, 25, 50, 100 ppm), revealed decrements in auditory function at PND22 and

12 permanent changes into adulthood using action potential (AP) testing (50 ppm). Together, these animal

13 studies demonstrated that in utero or perinatal exposure to CO can adversely affect adult behavior,

14 neuronal myelination, neurotransmission, and the auditory system in adult male rodents. Considering the

15 combined evidence from controlled human exposure and toxicological studies, **the evidence is**

16 **suggestive of a causal relationship between relevant short- and long-term CO exposures and**

17 **central nervous system effects.**

5.4. Birth Outcomes and Developmental Effects

5.4.1. Epidemiologic Studies

18 Although the body of literature is growing, the research focusing on adverse birth outcomes is

19 limited when compared to the numerous studies that have examined the more well-established health

20 effects of air pollution.Various dichotomized measures of birth weight, such as LBW, SGA, and IUGR,

21 have been the most examined outcomes in air pollution research while preterm birth (PTB), congenital

22 malformations, and infant mortality are less studied.

23 In the 2000 CO AQCD only two studies were cited that examined the effect of ambient air

24 pollution on adverse birth outcomes and both of these studies investigated LBW as an endpoint

25 (Alderman et al., 1987; Ritz and Yu, 1999). At that time this area of research was in its infancy and since

26 then there has been increasing interest.

5.4.1.1. Preterm Birth

1   A small number of air pollution-birth outcome studies have investigated the possible association
2   between PTB and maternal exposure to CO with the majority of U.S. studies conducted in southern
3   California. The earliest of these studies examined exposures to ambient CO during the first month of
4   pregnancy and the last 6 weeks prior to birth among a cohort of 97,158 births in southern California
5   between 1989 and 1993 (Ritz et al., 2000). The exposure assessment within this study was based on data
6   from fixed site monitors that fell within a 2-mile radius of the mother's ZIP code area. The crude relative
7   risks for PTB associated with a 1 ppm increase in 3-h avg CO concentration (6:00 to 9:00 a.m.) during the
8   last 6 weeks prior to birth and the first month of pregnancy were 1.04 (95% CI: 1.03-1.5) and 1.01
9   (95% CI: 1.00-1.03) respectively. However, when the authors controlled for other risk factors, only the
10   effect associated with CO during the last 6 weeks prior to birth persisted (RR: 1.02 [95% CI: 1.01-1.03]).
11   Furthermore, when the analyses included variables for either season or other pollutants the CO effect
12   estimates generally were reduced.
13   Expanding on this research, Wilhelm and Ritz (2005) examined PTB among a cohort of 106,483
14   births in Los Angeles County, CA between 1994 and 2000. Based on data recorded at monitoring stations
15   of varying proximities to the mother's residence, the main exposure windows examined were the first
16   trimester and the last 6 weeks prior to birth. Among women living within a 1-mile radius of a CO
17   monitoring station, a 0.5 ppm increase in 24-h avg CO concentration during the first trimester was
18   associated with a 3% (RR: 1.03 [95% CI: 1.00-1.06]) increased risk of PTB. This result persisted after
19   simultaneously adjusting for NO_2 and O_3 (RR: 1.05 [95% CI: 1.00-1.10]), but not with the inclusion of
20   PM_{10} into the regression model (RR: 0.99 [95% CI: 0.91-1.09]). The result from the single pollutant
21   model for CO exposures averaged over the 6 weeks prior to birth was similar in magnitude but failed to
22   reach statistical significance (RR: 1.02 [95% CI: 0.99-1.04]).
23   A limitation of many air pollution-birth outcome studies is the limited availability of detailed
24   information on maternal lifestyle factors and time-activity patterns during pregnancy. To assess possible
25   residual confounding due to these factors, Ritz and colleagues (Ritz et al., 2007) were able to analyze
26   detailed maternal information from a survey of 2,543 of 6,374 women sampled from a cohort of 58,316
27   eligible births in 2003 in Los Angeles County. Based on data from the closest monitor to the mother's ZIP
28   code area, exposures to CO, NO_2, O_3, and $PM_{2.5}$ during the first trimester and last 6 weeks prior to
29   delivery were examined and results from the overall cohort (n = 58,316) with limited maternal
30   information were compared to the more detailed nested case-control cohort (n = 2,543). Within the overall
31   cohort, CO during the first trimester was associated with an increased risk of 25% (OR: 1.25
32   [95% CI: 1.12-1.38]; highest exposure group >1.25 ppm vs. lowest ≤ 0.58 ppm). This result persisted
33   within the nested case-control cohort (OR: 1.21 [95% CI: 0.88-1.65]) where factors such as passive
34   smoking and alcohol use during pregnancy were included in the model; however, the confidence intervals

1   were wider due to the smaller sample. Any possible association between CO and PTB was less evident

2   during the last 6 weeks prior to birth. A strength of this study was that it also highlighted how there was

3   little change in the air pollution effect estimates when controlling for more detailed maternal information

4   (e.g., smoking, alcohol use), as opposed to only controlling for more limited maternal information that is

5   routinely collected on birth registry forms.

6   In contrast to the Los Angeles studies, a case-control study of PTB across California for the period

7   1999 through 2000 found a positive, though not statistically significant association, with 24-h CO

8   concentration during the entire pregnancy (OR: 1.03 [95% CI: 0.98-1.09] per 0.5 ppm increase), the first

9   month of gestation (OR: 1.05 [95% CI: 0.99-1.10] per 0.5 ppm increase), and the last 2 weeks of gestation

10   (OR: 1.00 [95% CI: 0.96-1.04] per 0.5 ppm increase) (Huynh et al., 2006). Although there was an

11   indication of an effect during early pregnancy, the small sample size (when compared to other studies)

12   may have influenced the lack of statistical significance. Furthermore, exposures within this study were

13   assigned based on a county-level average which may explain the lack of effect, given the poor level of

14   exposure assessment.

15   Studies outside of the U.S. have been conducted in Canada, Australia, and Korea with mixed

16   results reported. In Vancouver, Canada, based on a city-wide average across available monitoring sites,

17   24-h avg CO concentration during the last month of pregnancy was associated with a 4% (OR: 1.04

18   [95% CI: 1.00-1.07]) increased risk of PTB per 0.5 ppm increase while there was no association found

19   during the first month of pregnancy (OR: 0.98 [95% CI: 0.94-1.00]) (Liu et al., 2003). This study

20   investigated maternal exposures to ambient gaseous pollutants (CO, NO_2, SO_2, O_3) averaged over the first

21   and last month of pregnancy among a cohort of 229,085 births between 1985 and 1998.

22   In a cohort of 52,113 births in Incheon, Korea between 2001-2002, CO concentrations during the

23   first trimester was associated with a 26% (RR: 1.26 [95% CI: 1.11-1.44]) increased risk of PTB for the

24   highest quartile of exposure when compared to the lowest quartile (Leem et al., 2006). There was also a

25   strong significant trend exhibited across the quartiles. A similar result was found for 24-h avg CO

26   concentration during the last trimester although the effect was less pronounced (RR: 1.16

27   [95% CI: 1.01-1.24]). To assign the maternal exposures to CO, this study used a kriging technique, which

28   is a statistical mapping technique that allows the prediction of an average concentration over a spatial

29   region from data collected at specific points. The spatial average CO concentrations were then linked to

30   each study subject's residential address.

31   Conversely, a study in Sydney, Australia, examined maternal exposure to ambient air pollution

32   during the first and last month, and the first and last trimester of pregnancy among a cohort of 123,840

33   births between 1998-2000 and found no association between PTB and CO (Jalaludin et al., 2007).

34   Maternal exposure estimates in this study were based on a city-wide average of available monitoring sites

35   and also based on data from fixed sites within 5 km of the mother's postcode area. The odds ratios for

36   PTB associated with 8-h avg CO concentrations during the first trimester and last three months of

1 gestation were 1.18 (95% CI: 0.85-1.63) and 1.08 (95% CI: 0.95-1.22), respectively, when including

2 births within 5 km of a monitor. Interestingly, when all births were included in the analyses and the

3 exposure was based on a city-wide average, these effects had become protective for the first trimester

4 (OR: 0.82 [95% CI: 0.77-0.87]) and last three months of gestation (OR: 0.99 [95% CI: 0.92-1.07]). This

5 suggests that exposures based on data from fixed sites closer to the mother's address are more likely to

6 detect an effect than a city-wide average.

7   Figure 5-6 shows the risk ratios for the risk of delivering a preterm infant from the reviewed

8 studies. Table 5-12 provides a brief overview of the PTB studies. In summary there are mixed results

9 across the studies. Although these studies are difficult to compare directly due to the different exposure

10 assessment methods employed, there is some evidence that CO during early pregnancy (e.g., first month

11 and trimester) is associated with an increased risk of PTB. The most consistency is exhibited within the

12 studies conducted around Los Angeles, CA and surrounding areas whereby all studies reported a

13 significant association with CO exposure during early pregnancy, and exposures were assigned from

14 monitors within close proximity of the mother's residential address (Ritz et al., 2000; Ritz et al., 2007;

15 Wilhelm and Ritz, 2005). It should also be noted that the mixed results when analyzing different cohorts

16 that resided within varying proximities to a monitor may be attributable to analyzing different

17 populations.
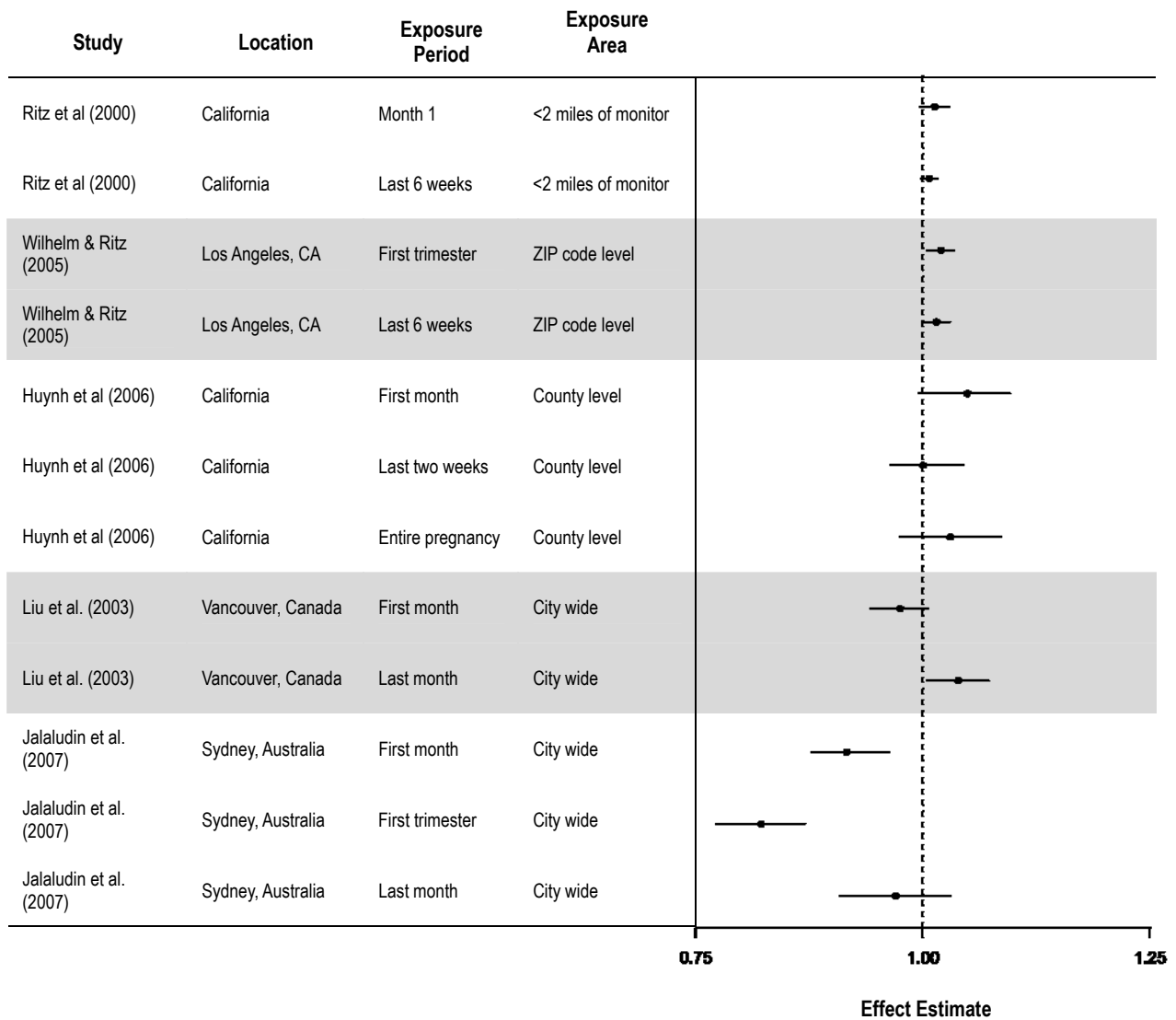
Figure 5-6. Summary of effect estimates (95% confidence intervals) for PTB associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-12.   Brief summary of PTB studies.

Study	Location (Sample Size)	Mean CO (ppm)	Exposure Assessment	Exposure Window
Ritz et al. (2000)	California (n = 97,158)	2.7 (6-9 a.m.)	<2 miles of monitor	Month 1 Last 6 weeks
Wilhelm and Ritz (2005)	Los Angeles, CA (n = 106,483)	1.4 (24 h)	Varying distances to monitor	Month 1 Last 6 weeks
Ritz et al. (2007)	Los Angeles, CA (n = 58,316)	0.87 (24 h)	Nearest monitor to ZIP code	Entire pregnancy Trimester 1 Last 6 weeks
Huynh et al. (2006)	California (n = 42,692)	0.8 (24 h)	County level	Entire pregnancy Month 1 Last 2 weeks
Liu et al. (2003)	Vancouver, Canada (n = 229,085)	1.0 (24 h)	City wide average	Month 1 Last month
Leem et al. (2006)	Incheon, Korea (n = 52,113)	0.9 (24 h)	Residential address within Dong-based on Kriging	First trimester Last trimester
Jalaludin et al. (2007)	Sydney, Australia (n = 123,840)	0.9 (8 h)	City wide average and <5 km from monitor	First month First trimester Last trimester Last month

5.4.1.2. Birth Weight, Low Birth Weight, and Intrauterine Growth Restriction/Small for Gestational Age

1   With birth weight routinely collected in vital statistics and a powerful predictor of infant mortality,

2   it is the most studied outcome within air pollution-birth outcome research. Air pollution researchers have

3   analyzed birth weight as a continuous variable, and/or as a dichotomized variable in the forms of low

4   birth weight (LBW) (<2,500g [5 lbs, 8 oz]) and SGA.

5   It should be noted that the terms small for gestational age (SGA), which is defined as a birth weight

6   <10th percentile for gestational age (and often sex), and intrauterine growth restriction (IUGR) are used

7   interchangeably. However, this definition of SGA does have limitations. For example, using this

8   definition of IUGR may overestimate the percentage of 'growth-restricted' neonates as it is unlikely that

9   10% of neonates have growth restriction (Wollmann, 1998). On the other hand, when the 10th percentile

10   is based on the distribution of live births at a population level the percentage of SGA among preterm

11   births is most likely underestimated (Hutcheon and Platt, 2008).

12   Nevertheless, the terms SGA and IUGR are often used interchangeably and it therefore should be

13   noted that SGA represents a statistical description of a small neonate, whereas the term IUGR is reserved

14   for those with clinical evidence of abnormal growth. Meaning that all IUGR neonates will be SGA, but

1   not all SGA neonates will be IUGR (Wollmann, 1998). In the following sections the terms SGA and

2   IUGR are referred to as each cited study used the terms.

3   Over the past decade a number of studies examined various metrics of birth weight in relation to

4   maternal exposure to CO with the majority conducted in the U.S. Given that most studies examined

5   multiple birth weight metrics, in order to avoid overlap of the studies the following section focuses on

6   each study only once and presents results for each metric within that study.

7   Most of the U.S. studies have been conducted in southern California with inconsistent results

8   reported with regard to gestational timing of the CO effects. The first of these studies was reviewed in the

9   2000 CO AQCD and is briefly summarized here. Ritz and Yu (1999) examined the effect of ambient CO

10   during the last trimester on LBW among 125,573 births in Los Angeles between 1989 and 1993. When

11   compared to neonates born to women in the lowest CO exposure group (<2.2 ppm), neonates born to

12   women in the highest exposure group (5.5 ppm - 95th percentile) had a 22% (OR: 1.22 [95% CI: 1.03-

13   1.44]) increased risk of being born as LBW.

14   Building upon this research, Wilhelm and Ritz (2005) reported similar results when extending this

15   study to include 136,134 births for the period of 1994–2000. Exposure to ambient CO during each

16   trimester was based on data recorded at monitoring stations of varying proximities to the mother's

17   residence. For women residing within 1 mile of a station, there was 36% (OR: 1.36 [95% CI: 1.04-1.76])

18   increased risk of having a term LBW baby for women in the highest CO exposure category

19   (1.84 ppm-75th percentile) for the third-trimester. There was also an increased risk of term LBW (OR:

20   1.28 [95% CI: 1.12-1.47]) among women in the highest exposure group when the analyses included

21   women within a 5 mile radius of a station. However, when the analyses included women within a 1-2

22   mile, or 2-4 mile radius of a station, the CO effects failed to reach statistical significance and there was no

23   evidence of an exposure-response pattern exhibited across the varying distances to a station. Furthermore,

24   none of the significant CO results persisted after controlling for other pollutants. Although standard errors

25   were certainly increased after controlling for the other pollutants leading to non-significant results, some

26   of the effect sizes were similar, providing some consistency. It is interesting to note, however, that

27   maternal exposure to CO during trimesters one and two was not associated with LBW (results not

28   reported).

29   Further validation in association with exposure times was observed in an analysis using a susbset of

30   participants in the Children's Health Study. Salam and colleagues (2005) found that CO only during the

31   first trimester was associated with reduced fetal growth. Their research examined birth weight, LBW, and

32   IUGR among a subset of participants in the Children's Health Study (Peters et al., 1999b) who were born

33   in California between 1975-1987 (n = 3901). The study examined term births with a gestational age

34   between 37-44 weeks. Exposures in this study were based on CO data from up to the three nearest

35   monitoring sites within 50 km of the centroid of the mother's ZIP code. Exposures for the entire

36   pregnancy and each trimester were analyzed and a 0.5 ppm increase in 24-h CO concentration during the

1 first trimester was associated with a 7.8 g (95% CI: 15.1-0.4) decrease in birth weight, which also

2 translated to a 6.7% (OR: 1.07 [95% CI: 1.00-1.13]) increased risk of IUGR; however, there was no

3 significant association with LBW (OR: 1.00 [95% CI: 0.88-1.16]).

4   In contrast to the previous studies, another California study of 18,247 singleton births born at 40

5 weeks gestation during 2000 found no association between ambient 24-h CO concentration and reduced

6 birth weight or SGA where the highest quartile of exposure was 0.98 ppm. Based on data from fixed sites

7 within 5 miles of the mother's residence, exposures to CO and $PM_{2.5}$ during the entire pregnancy and each

8 trimester were analyzed. Although CO during the entire pregnancy was associated with a 20 g

9 (95% CI: 40.1-0.8) reduction in birth weight, this did not persist after controlling for $PM_{2.5}$. $PM_{2.5}$ was

10 found to have a strong effect on birth weight within each trimester (Parker et al., 2005).

11   Two similar studies were conducted in the Northeast of the U.S. with inconsistent results. A study

12 of 89,557 singleton term births in Boston, MA, Hartford, CT, Philadelphia, PA, Pittsburgh, PA, and

13 Washington, DC between 1994-1996 found that exposure to ambient CO during the third trimester was

14 associated with an increased risk of LBW (OR: 1.14 [95% CI: 1.03-1.27] per 0.5 ppm increase) (Maisonet

15 et al., 2001). When stratified by race this effect was only significant among African Americans for the

16 first and third trimesters (First OR: 1.32 [95% CI: 1.22-1.43]; Third OR: 1.20 [95% CI: 1.09-1.32]).

17 Exposures to PM_{10} and SO_2 were examined and there was no strong evidence that these pollutants were

18 associated with LBW. Exposures for this study were based on a city-wide average of monitors within the

19 mother's city of residence. The second study examined 358,504 births at 32-44 weeks gestation between

20 1999-2002 in Connecticut and Massachusetts (Bell et al., 2007). 24-h CO exposures were estimated from

21 fixed sites within each mother's county of residence (e.g., county level). CO averaged over the entire

22 pregnancy was associated with a reduction in birth weight of 27.0 g (95% CI: 21.0-32.8). This result

23 persisted after controlling for each additional pollutant (PM_{10}, $PM_{2.5}$, NO_2, and SO_2) in two-pollutant

24 models. However, this reduction in birth weight did not translate to an increased risk of LBW (OR: 1.05

25 [95% CI: 0.97-1.12]). When controlling for exposure during each trimester, the reduction in birth weight

26 associated with a 0.5 ppm increase in 24-h CO concentration during the first trimester ranged from 18.8 to

27 16.5 g while the reductions associated with third trimester exposure ranged between 23.3 and 27.2 g. It is

28 interesting to note that, although the exposures were based on data averaged at the county level, CO was

29 associated with a reduction in birth weight. Whereas, in a previously cited California study by Huynh and

30 colleagues (Huynh et al., 2006) exposures were also at the county level yet there was no association with

31 PTB. This difference may be due to the counties being smaller in New England than in California,

32 resulting in more precise exposure estimates.

33   Two studies in Canada investigated the effects of ambient air pollution on fetal growth with

34 exposures derived from a city-wide average across the available monitoring sites. The first of these

35 studies was among a cohort of 229,085 singleton term births (37-42 weeks gestation) in Vancouver, BC

36 with monthly and trimester exposures to CO investigated in relation to LBW and IUGR (Liu et al., 2003).

1   For a 0.5 ppm increase in 24-h CO concentration during the first month of pregnancy there was an

2   increased risk of IUGR (OR: 1.03 [95% CI: 1.00-1.05]) and this was of borderline significance when CO

3   was averaged over the first trimester (OR: 1.02 [95% CI: 1.00-1.05]). This result persisted after

4   controlling for other gaseous pollutants. Conversely, maternal exposure to CO was not associated with

5   LBW. The more recent of these 2 studies examined 386,202 singleton term births (37-42 weeks gestation)

6   in Calgary, Edmonton and Montreal between 1986 and 2000 (Liu et al., 2007). The study examined

7   monthly and trimester exposures to CO with IUGR being the only endpoint. A 0.5 ppm increase in 24-h

8   CO concentration was associated with an increased risk of IUGR in the first (OR: 1.09

9   [95% CI: 1.07-1.11]), second (OR: 1.07 [95% CI: 1.05-1.09]), and third trimesters (OR: 1.09

10   [95% CI: 1.07-1.11]) of pregnancy. This result translated to CO exposure having a positive effect on

11   IUGR within each individual month of pregnancy with the highest effect during the first and last months.

12   This result persisted after controlling for concurrent NO_2 and $PM_{2.5}$.

13   Two studies in Sao Paulo, Brazil, a city with notably high levels of air pollution (mean CO

14   3.7 ppm) investigated associations between maternal exposures to CO in relation to reduced birth weight

15   and LBW within two consecutive time periods and found similar results. In both studies the exposures

16   were derived from a city-wide average across the available monitoring sites. The first study examined

17   179,460 singleton term births during 1997 and found that a 0.75 ppm increase in 8-h CO concentration

18   averaged over the first trimester was associated with a 17.3 g (95% CI: 31.0-3.7) reduction in birth weight

19   (Gouveia et al., 2004). The second of these studies examined 311,735 singleton births (37-41 weeks

20   gestation) between 1998 and 2000 and reported a 6.0 g reduction in birth weight associated with a

21   0.5 ppm increase in 24-h CO concentration averaged over the first trimester (Medeiros and Gouveia,

22   2005). It is important to note that neither of these studies found an association between CO exposure and

23   an increased risk of LBW. Therefore, despite CO during the first trimester being associated with reduced

24   birth weight, it was not associated with LBW.

25   Similar to the two studies in Sao Paulo, Brazil, researchers in Seoul, South Korea conducted two

26   studies using data from two consecutive time periods. Both of these studies based the exposure estimates

27   on a city-wide average from all available fixed sites and as would be expected, the results pertaining to

28   CO were similar for both studies. For example, Ha and colleagues (2001) examined maternal exposures to

29   CO during the first and third trimesters among 276,763 singleton term births in Seoul between 1996 and

30   1997. Exposure to CO during the first trimester was associated with a decrease in birth weight of 13.3 g,

31   which also translated into an increased risk of LBW (RR: 1.10 [95% CI: 1.05-1.14] per 0.5 ppm increase

32   in 24-h CO concentration). When Lee and colleagues (2003a) extended this study to include singleton

33   term births (37-44 weeks gestation) for the period of 1996 to 1998 with 24-h CO concentrations averaged

34   over each month of pregnancy and trimester, CO exposure during the first trimester was associated with

35   an increased risk of LBW (OR: 1.04 [95% CI: 1.01-1.07] per 0.5 ppm increase). No associations were

1   found in the third trimester for any of the pollutants. Monthly-specific exposures showed that the risk of

2   LBW tended to increase with CO exposure between months 2-5 of pregnancy.

3   In contrast to other studies reporting that early and late pregnancy are the critical periods for CO

4   exposure, a Sydney, Australia study of 138,056 singleton births between 1998-2000 reported a reduction

5   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

6   increase in maternal exposure to 8-h CO averaged over the second and third trimesters respectively

7   (Mannes et al., 2005). However, this result did not persist after controlling for other pollutants (PM_{10},

8   NO_2) and was only significant when including births where the mother resided within 5 km of a monitor.

9   Furthermore, this result did not translate to an increased risk of SGA, which was defined as a birth weight

10   two standard deviations below the mean. The odds ratios for SGA for CO exposures during the first,

11   second and third trimesters were 0.96 (95% CI: 0.91-1.03), 0.99 (95% CI: 0.92-1.07), and 1.01

12   (95% CI: 0.93-1.08) respectively. While the majority of studies restrict the analyses to term births as a

13   method of controlling for gestational age, it is important to note that the Sydney study used all births and

14   controlled for gestational age in the birth weight analyses and SGA was derived from each gestational age

15   group.

16   Of all studies reviewed, only two failed to find an association between maternal exposure to CO

17   and adverse birth outcomes. In northern Nevada, Chen and colleagues (2002) examined CO, PM_{10}, and O_3

18   exposures among a cohort of 39,338 term births (37-44 weeks gestation) between 1991 and 1999 and

19   found no association between CO exposure during the entire pregnancy (and each trimester) and a

20   reduction in birth weigh or an increased risk of LBW. For a 0.75 ppm increase in 8-h CO concentration

21   averaged over the entire pregnancy there was a reduction in birth weight of 6 g, however it failed to reach

22   statistical significance. Exposures for this study were based on data from all monitoring sites across

23   Washoe County, Nevada.

24   In a retrospective cohort study among 92,288 singleton term births (37-44 weeks gestation) in

25   Taipei and Kaoshiung, Taiwan between 1995-1997, maternal exposures to CO, SO_2, O_3, NO_2, and PM_{10} in

26   each trimester of pregnancy were examined and only SO_2 during the third trimester showed evidence of

27   attributing to LBW. Exposure assessment was based on data from the monitor closest to the centroid of

28   the mother's residential district and the final analyses only included mothers whose district centroid was

29   within 3 km of a monitor. CO exposures were grouped into low (~1.1 ppm), medium (~1.2-15.0 ppm),

30   and high (>15.0 ppm) and when compared to the lowest exposure group, the odds ratio for LBW in the

31   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

32   the second trimester, and 0.86 (95% CI: 0.71-1.03) for the third trimester (Lin et al., 2004a).

33   Table 5-13 provides a brief overview of the birth weight studies. In summary, there is evidence of

34   ambient CO during pregnancy having a negative effect on fetal growth. From the reviewed studies

35   Figure 5-7 shows the change in birth weight (grams), Figure 5-8 shows the effect estimates for LBW, and

36   Figure 5-9 shows the effect estimates for SGA. In general the reported reductions in birth weight are

1   small (ranging ~10-20g). It is difficult to conclude whether CO is related to a small change in birth weight

2   in all births across the population, or a marked effect in some subset of births.

3   Furthermore, there is a large degree of inconsistency across these studies. This may be due to

4   several factors such as inconsistent exposure assessment and statistical methods employed, different CO

5   concentrations, and/or different demographics of the birth cohorts analyzed. The main inconsistency

6   among these findings is the gestational timing of the CO effect. Although the majority of studies reported

7   significant effects during either the first or third trimester, other studies failed to find a significant effect

8   during these periods. Several studies found an association with exposure during the entire pregnancy,

9   providing evidence for a possible accumulative effect; however, these results are inconclusive and this

10   may be the result of correlated exposure periods.

11   Several studies examined various combinations of birth weight, LBW, and SGA/IUGR and

12   inconsistent results are reported across these metrics. For example, several studies reported an association

13   between maternal exposure to CO and decreased birth weight yet the decrease in birth weight did not

14   translate to an increased risk of LBW or SGA. However, it needs to be noted that a measureable change,

15   even if only a small one, on a population is different than an effect on a subset of susceptible births which

16   may increase the risk of IUGR/LBW/SGA.

17   The possibility exists that the small reductions in birth weight associated with maternal CO

18   exposures are the result of residual confounding associated with other factors (e.g., other pollutants,

19   temperature, and spatial/temporal variation in maternal factors) or other correlated pollutants. For

20   example, in some studies the CO effect did not persist after controlling for other pollutants (Mannes et al.,

21   2005; Parker et al., 2005; Wilhelm and Ritz, 2005) while in some studies it did persist (Bell et al., 2007;

22   Gouveia et al., 2004; Liu et al., 2003, 2007), and other studies did not report results from multipollutant

23   models (Ha et al., 2001; Lee et al., 2003a; Maisonet et al., 2001; Medeiros and Gouveia, 2005). In

24   addition, various methods have been employed to control for seasonality and trends (e.g., month of birth,

25   season of birth, year of birth, smoothed function of time), which may explain some of the mixed results.

26   The two U.S. studies conducted in the Northeast compared results from analyses stratified by race.

27   The earlier of these studies found an association between CO and LBW among African Americans but not

28   among whites and hispanics (Maisonet et al., 2001). In contrast, despite reporting an 11g reduction in

29   birth weight among African-Americans and a 17 g reduction among whites, the more recent of the two

30   studies found no significant difference between these reductions by race (Bell et al., 2007). Parker and

31   colleagues (2005) also tested for interactions between race and found no significant association.

Study	Location	Exposure Period	Exposure Area
Bell et al (2007)	Connecticut & Massachusetts	Entire pregnancy	County level
Salam et al. (2005)	California	First trimester	ZIP code level
Salam et al. (2005)	California	Second trimester	ZIP code level
Salam et al. (2005)	California	Third trimester	ZIP code level
Salam et al. (2005)	California	Entire pregnancy	ZIP code level
Chen et al. (2002)	Northern NV	First trimester	County level
Chen et al. (2002)	Northern NV	Second trimester	County level
Chen et al. (2002)	Northern NV	Third trimester	County level
Chen et al. (2002)	Northern NV	Entire pregnancy	County level
Mannes et al. (2005)	Sydney, Australia	First trimester	City level
Mannes et al. (2005)	Sydney, Australia	Second trimester	City level
Mannes et al. (2005)	Sydney, Australia	Third trimester	City level
Mannes et al. (2005)	Sydney, Australia	Last month	City level
Gouveia et al. (2004)	Sao Paulo, Brazil	First trimester	City level
Gouveia et al. (2004)	Sao Paulo, Brazil	Second trimester	City level
Gouveia et al. (2004)	Sao Paulo, Brazil	Third trimester	City level
Medeiros et al. (2005)	Sao Paulo, Brazil	First trimester	City level
Medeiros et al. (2005)	Sao Paulo, Brazil	Second trimester	City level
Medeiros et al. (2005)	Sao Paulo, Brazil	Third trimester	City level

Figure 5-7. 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.

Author	Location	Exposure Period	Exposure Area
Bell et al (2007)	Connecticut & Massachusetts	Entire pregnancy	County level
Maisonet et al. (2001)	Northeastern USA	First trimester	City level
Maisonet et al. (2001)	Northeastern USA	Second trimester	City level
Maisonet et al. (2001)	Northeastern USA	Third trimester	City level
Wilhelm and Ritz (2005)	Los Angeles County, CA	Third trimester	ZIP code level
Salam et al. (2005)	California	First trimester	ZIP code level
Salam et al. (2005)	California	Second trimester	ZIP code level
Salam et al. (2005)	California	Third trimester	ZIP code level
Salam et al. (2005)	California	Entire pregnancy	ZIP code level
Liu et al. (2003)	Vancouver, Canada	First month	City level
Liu et al. (2003)	Vancouver, Canada	Second month	City level
Ha et al (2001)	Seoul, Korea	First trimester	City level
Ha et al (2001)	Seoul, Korea	Third trimester	City level
Lee et al. (2003a)	Seoul, Korea	First trimester	City level
Lee et al. (2003a)	Seoul, Korea	Second trimester	City level
Lee et al. (2003a)	Seoul, Korea	Third trimester	City level
Lee et al. (2003a)	Seoul, Korea	Entire pregnancy	City level

Figure 5-8. 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.
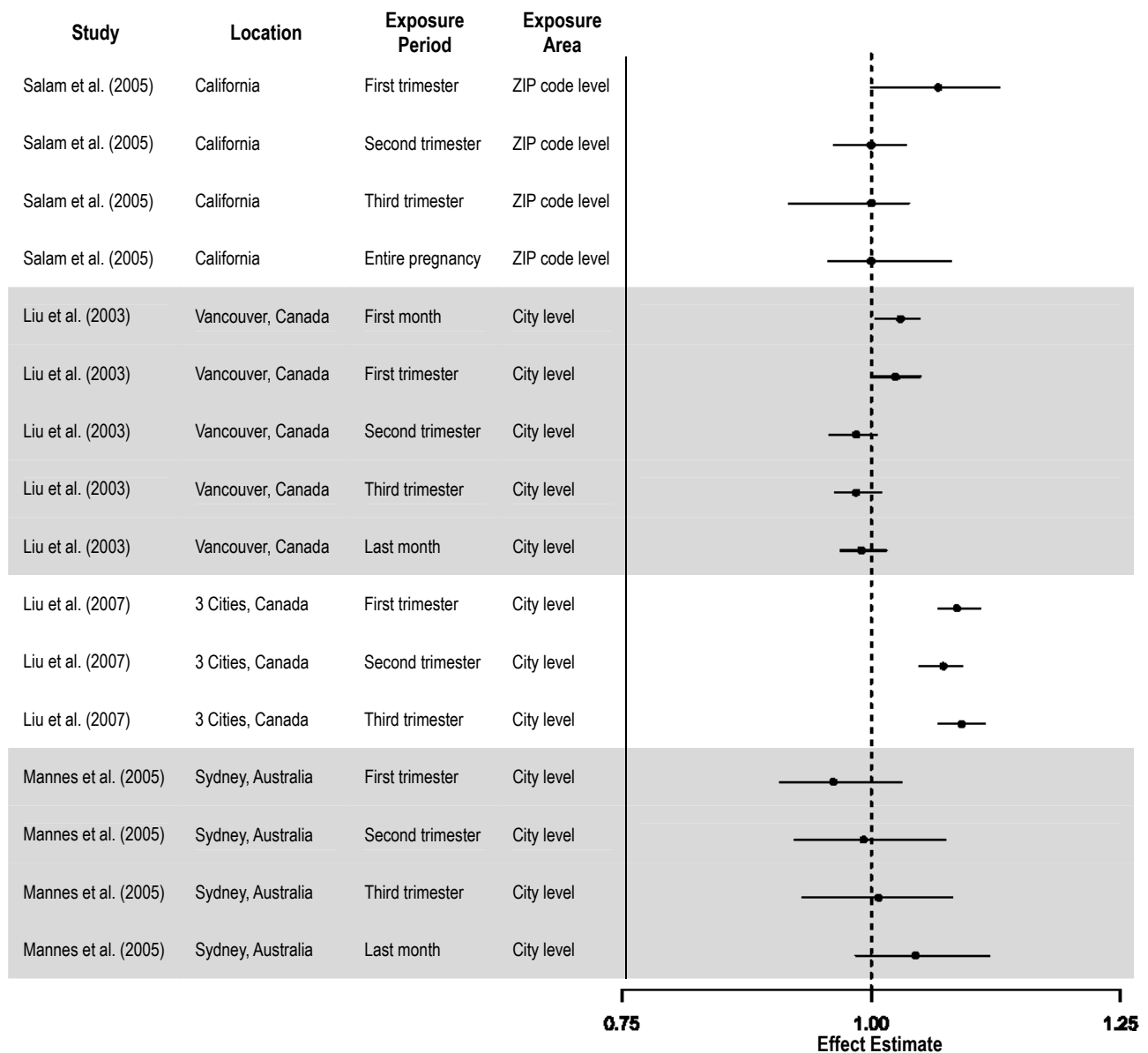
Figure 5-9. Summary of effect estimates (95% confidence intervals) for SGA associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

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)	LBW	Los Angeles, CA (n = 125, 573)	2.6 (6-9 a.m.)	<2 miles of monitor	Trimester 3
Wilhelm and Ritz (2005)	LBW	Los Angeles County, CA (n = 136, 134)	1.4 (24 h)	Varying distances from monitor	Trimesters 1, 2, 3
Salam et al. (2005)	Birth weight LBW IUGR	California (n = 3901)	1.8 (24 h)	ZIP code level	Entire pregnancy Trimesters 1, 2, 3
Parker et al. (2005)	Birth weight SGA	California (n = 18,247)	0.75 (8 h)	<5 miles from monitor	Entire pregnancy Trimesters 1, 2, 3
Maisonet et al. (2001)	LBW	Boston, MA; Hartford, CT; Philadelphia & Pittsburg, PA; Washington DC (n = 103,465)	1.1 (24 h)	City wide average	Trimesters 1, 2, 3
Bell et al. (2007)	Birth weight LBW	Connecticut and Massachusetts, (n = 358,504)	0.6 (24 h)	County level average	Entire pregnancy Trimesters 1, 3
Chen et al. (2002)	Birth weight LBW	Northern Nevada, (n = 36,305)	0.9 (8 h)	County level	Trimesters 1, 2, 3
CANADA					
Liu et al. (2003)	LBW IUGR	Vancouver, Canada (n = 229,085)	1.0 (24 h)	City wide average	Trimester 1
Liu et al. (2007)	IUGR	Calgary, Edmonton, Montreal, Canada (n = 386,202)	1.1 (24 h)	City wide average	Trimesters 1, 2, 3
SOUTH AMERICA					
Gouveia et al. (2004)	Birth weight LBW	Sao Paulo, Brazil (n = 179,460)	3.7 (8 h)	City wide average	Trimesters 1, 2, 3
Medeiros et al. (2005)	Birth weight LBW	Sao Paulo, Brazil (n = 311,735)	3.0 (24 h) (Presented in graph)	City wide average	Trimesters 1, 2, 3
AUSTRALASIA					
Ha et al. (2001)	Birth weight LBW	Seoul, Korea (n = 276,763)	1.2 (24 h)	City wide average	Trimesters 1 and 3
Lee et al. (2003a)	LBW	Seoul, Korea (n = ?)	1.2 (24 h)	City wide average	Entire pregnancy Trimesters 1, 2, 3
Mannes et al. (2005)	Birth weight SGA	Sydney, Australia (n = 138,056)	0.8 (8 h)	City wide average and <5 km from monitor	Trimesters 1, 2, 3 Last 30 days
Lin et al. (2004b)	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

1   Despite the growing evidence of an association between ambient air pollution and various adverse
2   birth outcomes, only three studies investigated the effect of temporal variations in ambient air pollution
3   on congenital anomalies. Given the higher prevalence and associated mortality, heart defects have been
4   the main focus of two of these three recent air pollution studies. The other study's focus was cleft
5   lip/palate.
6   The first of these studies was conducted in southern California (Ritz et al., 2002). Exposure to
7   ambient CO, NO_2, O_3 and PM_{10} during each of the first three months of pregnancy was examined among
8   births during 1987-1993. Maternal exposure estimates were based on data from the fixed site closest to
9   the mother's ZIP code area and when using a case-control design where cases were matched to 10
10   randomly selected controls, results showed that CO during the second month of pregnancy was associated
11   with cardiac ventricular septal defects. The CO exposures were grouped by quartiles (25th = 1.14,
12   50th = 1.57, 75th = 2.39 ppm) and when compared to those in the lowest quartile exposure group
13   (<1.14 ppm), the odds ratios for ventricular septal defects across the 3 exposure groups were 1.62
14   (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
15   multipollutant model a similar exposure-response pattern was exhibited across the quartiles with the
16   highest quartile of exposure reaching statistical significance (OR: 2.84 [95% CI: 1.15-6.99]). The only
17   other pollutant associated with a defect was O_3 during the second month of pregnancy, which was
18   associated with aortic artery and valve defects.
19   The second study was conducted in Texas (Gilboa et al., 2005), where exposure to ambient CO,
20   NO_2, SO_2, O_3 and PM_{10} during the 3rd to 8th week of gestation was examined among births between
21   1997-2000. Maternal exposure estimates were calculated by assigning the data from the closest monitor to
22   the mother's residential address. If data were missing on a particular day then data from the next closest
23   site were used. The median distances from a monitor ranged from 8.6-14.2 km with maximum distances
24   ranging from 35.5-54.5 km. The main results showed that CO was associated with multiple conotruncal
25   defects and Tetralogy of Fallot. CO exposures were grouped into quartiles of much lower concentrations
26   (25th = 0.4, 50th = 0.5, 75th = 0.7 ppm) than the California study and when compared to the lowest
27   quartile, the odds ratios for conotruncal defects across the 3 CO exposure groups were 1.38
28   (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
29   test for trend (p for trend = 0.0870). Whereas, a strong exposure-response pattern was exhibited across
30   the quartiles of CO exposure for Tetralogy of Fallot (25th OR: 0.82 [95% CI: 0.52-1.62]; 50th OR: 1.27
31   [95% CI: 0.75-2.14]; 75th OR: 2.04 [95% CI: 1.26-3.29]; p for trend = 0.0017). The only significant
32   associations found with other pollutants were between PM_{10} and isolated atrial septal defects, and SO_2
33   and ventricular septal defects.

1   The last of these three studies was a case-control study that examined maternal exposure to various

2   air pollutants during the first three months of pregnancy and the risk of delivering an infant with an oral

3   cleft, namely cleft lip with or without palate (CL/P). Birth data from the Taiwanese birth registry from

4   2001 to 2003 was linked to air pollutant data that were spatially interpolated from all fixed monitoring

5   sites across Taiwan. Based on data at the center of the townships or districts, exposure estimates for PM_{10},

6   SO_2, NO_X, O_3, and CO were averaged over each of the first three months of pregnancy. Interestingly, of

7   all the pollutants examined, only O_3 during the first two months of pregnancy was significantly associated

8   with an increased risk of CL/P. In multipollutant models CO was not associated with CL/P (Hwang and

9   Jaakkola, 2008).

10   The main results from the southern California study showed that CO was associated with an

11   increased risk of ventricular septal defects and this was exhibited by an exposure-response pattern across

12   the quartiles of exposure, yet there was no indication that ambient CO concentration in Texas was

13   associated with ventricular septal defects. Conversely, ambient CO concentration in Texas was associated

14   with an increased risk of conotruncal defects, yet there was no indication that CO in southern California

15   was associated with conotruncal defects, and on the contrary, reported results of a protective effect.

16   Interestingly, similar inconsistencies were also found for PM_{10} between these studies. For example,

17   PM_{10} in Texas was associated with an increased risk of atrial septal defects, yet there was no indication of

18   such an effect in southern California where PM_{10} concentrations were markedly higher.

19   The authors of the Texas study (Gilboa et al., 2005) provide little discussion toward the

20   inconsistent results with the southern California study. One suggestion is the different CO concentrations

21   across the studies with the 75th quartile in southern California being 2.39 ppm while in Texas it was much

22   lower at 0.7 ppm. However, this suggests that different defects are associated with different

23   concentrations of CO, yet it still does not explain why particular associations were reported in Texas and

24   not southern California where concentrations were higher. Similarly, the authors of the Texas study

25   (Gilboa et al., 2005) also suggested the inconsistency was due to different exposure periods. In Texas the

26   exposures were averaged over the 3rd to 8th week while in southern California the exposures were

27   averaged over the second month of pregnancy. However, there was no reason provided as to why this

28   small difference in the examined exposure period would explain the inconsistent results.

29   Overall, there is little evidence that maternal exposure to CO is associated with an increased risk of

30   congenital anomalies, namely heart defects and cleft lip and palate. Further research is required to

31   corroborate these findings.

5.4.1.4. Neonatal and Post-Neonatal Mortality

1   A handful of studies examined the effect of ambient air pollution on neonatal and post-neonatal
2 mortality with the former the least studied. These studies varied somewhat with regard to the outcomes
3 and exposure periods examined, and study designs employed.

Neonatal

4   In Sao Paulo, Brazil, a time-series study examined daily counts of neonatal (up to 28 days after
5 birth) deaths for the period of 1998-2000 in association with concurrent day exposure to SO_2, CO, O_3,
6 PM_{10}. Moving averages from 2 to 7 days were examined. The mean city-wide CO concentration was
7 2.8 ppm and there was no association between daily ambient CO and neonatal deaths. Despite CO being
8 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
9 the daily rate of neonatal deaths (Lin et al., 2004a).

Post-Neonatal

10   Two studies in the U.S. examined the potential association between ambient CO and post-neonatal
11 (from 28 days to 1 year after birth) mortality and inconsistent results were reported. These studies,
12 however, varied somewhat in study design.
13   The first of these studies employed a case-control design and examined all infant deaths during the
14 first year of life among infants born alive during 1989-2000 within 16 km from a monitoring site within
15 the South Coast Air Basin of California. Exposures for 2-week, 1-month, 2-month, and 6-month periods
16 before death were linked to each individual death. Extensive analyses were conducted for all-cause infant
17 deaths, respiratory causes of death, and sudden infant death syndrome (SIDS). Given the long time period
18 of the data analyzed, in order to alleviate the confounding trends in infant mortality and CO levels this
19 study was able to match by year (Ritz et al., 2006). Ambient 1-h max CO concentrations averaged over
20 the 2 months before death were associated with an 11% (OR: 1.11 [95% CI: 1.06-1.16]) increase in risk of
21 all-cause post-neonatal death (per 1 ppm increase) and a 19% (OR: 1.19 [95% CI: 1.10-1.28]) increase in
22 risk of SIDS. In the multipollutant models (including PM_{10}, NO_2, O_3) the positive CO mortality effect
23 decreased by around 50% and failed to reach statistical significance. Based on exposure from 2 weeks
24 before death, CO was associated with an increased risk of respiratory related post-neonatal deaths
25 occurring 28 days to 1 year after birth (OR: 1.14 [95% CI: 1.03-1.25] per 1 ppm increase) and 28 days to
26 3 months after birth (OR: 1.20 [95% CI: 1.02-1.40]), but no effect was observed for respiratory related
27 deaths occurring 4-12 months after birth. These results persisted in the multipollutant models and
28 exposure-response patterns were exhibited across the exposures groupings of 1.02 to <2.08, and
29 $\geq$ 2.08 ppm. To control for gestational age and birth weight the analyses were stratified by 'term/normal-
30 weight infants' and 'preterm and/or LBW infants.' When these two strata were analyzed, CO was

1   associated with an increased risk of all-cause death and SIDS within both strata (ORs ranged from 1.12 to

2   1.46). However, these effects did not persist in multipollutant models (Ritz et al., 2006).

3   The second of these 2 studies examined 3,583,495 births, including 6,639 post-neonatal deaths

4   occurring in 96 counties throughout the U.S. (in counties with more than 250,000 residents) between

5   1989 and 2000 (Woodruff et al., 2008). Only exposure during the first two months of life was examined

6   and these were based on an average of CO concentrations recorded across all available monitors within

7   the mother's county of residence. In contrast to the other postnatal mortality study in California, CO

8   averaged over the first two months of life was not associated with all-cause death (OR: 1.01

9   [95% CI: 0.94-1.09] per 0.5 ppm increase in 24-h CO concentration), or with respiratory related deaths

10   (OR: 1.08 [95% CI: 0.91-1.54] per 0.5 ppm increase in 24-h CO concentration), SIDS (OR 0.85

11   [95% CI: 0.70-1.04] per 0.5 ppm increase in 24-h CO concentration), or other causes of post-neonatal

12   mortality (OR: 1.03 [95% CI: 0.96-1.09] per 0.5 ppm increase in 24-h CO concentration). These null

13   findings may be due to higher error of the exposure assessment at the county-level as opposed to using

14   data from monitors within close proximity to the residence.

15   The only other postnatal mortality studies have been conducted throughout Asia. Two identical

16   studies in Taiwan failed to find an association between daily counts of post-neonatal deaths and ambient

17   air pollutants, including CO. The data analyzed were from the cities of Taipei (Yang et al., 2006) and

18   Kaohsiung (Tsai et al., 2006b) with ambient CO concentrations being 1.6 ppm and 0.8 ppm respectively.

19   Both studies examined deaths for the period of 1994-2000 and employed a case-crossover design that

20   compared air pollution levels 1 week before and after each infant's death.

21   Similarly, another study in South Korea examined post-neonatal mortality for the period of 1995-

22   1999 using a time-series design. Same-day CO was not associated with all-cause death (RR: 1.02

23   [95% CI: 0.97-1.06] per 0.5 ppm increase). However, same-day CO was associated with post-neonatal

24   mortality when the analyses were restricted to respiratory mortality (RR: 1.33 [95% CI: 1.01-1.76] per

25   0.5 ppm increase) (Ha et al., 2003).

26   In general, the inconsistent exposure periods examined among these studies allows for limited

27   direct comparison and interpretation. Nevertheless, there is limited evidence that CO is associated with an

28   increased risk of infant mortality during the post-neonatal period. The exposure periods examined varied

29   from the same-day CO to lag periods up to a 6 month period prior to birth with one study alternatively

30   exploring exposures averaged over the first two months of life. Furthermore, given that birth weight and

31   gestational age are strong predictors of infant mortality, in all of the reviewed studies these factors have

32   not been considered at either the design or analysis stage. Hence, the link between fetal exposures,

33   neonatal exposures, and post-neonatal exposures, and the possible interaction that birth weight and

34   gestational age may have on the results yielded from these examined exposure periods, needs further

35   attention within this field of research.

5.4.1.5. Summary of Epidemiologic Studies of Birth Outcomes and Developmental Effects

1   There is some evidence that CO during early pregnancy (e.g., first month and first trimester) is

2   associated with an increased risk of PTB. Only two studies examined the effects of CO on birth defects.

3   Both studies found maternal exposure to CO to be associated with an increased risk of cardiac birth

4   defects. This insult to the heart is coherent with the CO effects on the heart characterized in Section 5.2.

5   In general, there is limited evidence that CO is associated with an increased risk of infant mortality during

6   the post-neonatal period.

7   There is evidence of ambient CO during pregnancy having a negative effect on fetal growth. In

8   general, the reviewed studies (Figures 5.7 through 5.9) reported small reductions in birth weight (ranging

9   ~10-20 g). Although the majority of studies reported significant effects during either the first or third

10   trimester, other studies failed to find a significant effect during these periods. Several studies examined

11   various combinations of birth weight, LBW, and SGA/IUGR and inconsistent results are reported across

12   these metrics. For example, six studies reported an association between maternal exposure to CO and

13   decreased birth weight yet the decrease in birth weight did not translate to an increased risk of LBW or

14   SGA. It should be noted that having a measurable, even if small, change in a population is different than

15   having an effect on a subset of susceptible births, which may increase the risk of IUGR/LBW/SGA. It is

16   difficult to conclude if CO is related to a small change in birth weight in all births across the population,

17   or a marked effect in some subset of births.

5.4.2. Toxicological Studies of Birth Outcomes and Developmental Effects

5.4.2.1. Birth Outcomes

Decreased Birth Weight

18   Multiple reports have been published associating low level CO exposure in laboratory animals and

19   decrements in birth weight; some of these studies noted reduced growth rates persisting in the neonatal

20   period. Prigge et al. (1977) saw significant decreases in near-term fetal body weight (GD21) after 21 days

21   of continuous exposure of pregnant Wistar rats to CO (125, 250, or 500 ppm). Fechter and Annau (1977)

22   exposed pregnant rats to 150 ppm CO continuously during gestation via inhalation and found 5%

23   significantly decreased birth weights at PND1 in gestationally exposed pups versus control animals with

24   weight decrements persisting to weaning; lactational cross fostering did not ameliorate the reduced

25   growth rates. Dams exposed to CO during gestation had COHb over gestation of 15% with control dams

1   having less than 1%. Decreased birth weight and pre-weaning weight were seen in CO-exposed pups

2   despite a lack of weight decrement in CO-exposed dams versus air-exposed control dams.

3   Penney et al. (1983) exposed pregnant rats to CO (157, 166, and 200 ppm) over GD6-GD19 and

4   found significant decreases in near term fetal rat weight at GD20; gestation in rats is ~ 22 days. Carmines

5   et al. (2008) exposed Sprague-Dawley rats to ~600 ppm CO via nose-only inhalation (levels similar to

6   those seen in cigarette smoke) during GD6-GD19 of gestation for 2 h/day and found significant decreases

7   in birth weight (0.5 g or 13%) of exposed pups versus controls. Dam COHb was 30% immediately after

8   exposure. The half life in rats at this exposure level is ~ 42 minutes. Maternal body weight was

9   unchanged during gestation, but corrected terminal body weight (body weight minus uterine weight) was

10 significantly elevated in CO-exposed dams at term. There were no external malformations (teratogenicity)

11 seen. Singh et al. (1992; 2006) found significant decreases in birth weight in gestationally CO-exposed

12 mouse pups (65, 125, 250 or 500 ppm) in two studies. In the 2006 study, mice were exposed to CO for 6

13 h/day for the first 2 weeks of pregnancy, and in the 1992 sutdy, dams were exposed to CO (GD0-GD18)

14 longer with fetuses collected at GD18. Astrup et al. (1972) found significant decreases (11 and 20%,

15 respectivelty) in birth weight of rabbits exposed to either 90 or 180 ppm CO continuously over the

16 duration of gestation. Fechter and Annau (1977) reported decreased birth weight, albeit not significant, of

17 Long-Evans rats exposed in utero to 150 ppm CO continuously throughout gestation (dam COHb 15%),

18 but by PND4 and through pre-weaning to PND21, exposed pups weighed significantly less than controls.

19 Tolcos et al. (2000a) found significant decreases in body weight and crown to rump length in guinea pig

20 fetuses after being exposed to 200 ppm CO for 10h/day from GD23-GD25 until GD61-GD63, at which

21 time the fetuses were collected (term ranges from GD68 to GD72). However, in other studies, Tolcos

22 found no significant differences in birth weight of guinea pig pups after a similar exposure (GD23-GD25

23 to term). During pregnancy, fetal and maternal COHb levels were 13% and 8.5%, respectively.

Pregnancy Loss and Perinatal Death

24   Schwetz et al. (1979) exposed CF-1 mice or New Zealand rabbits to 250 ppm CO for either 7 h/day

25 or 24 h/day over GD6-GD15 (mice) or GD6-GD18 (rabbits), yielding 4 exposure paradigms. The fetuses

26 were then collected by C-section at the termination of exposure, which was near term. Maternal COHb in

27 the 7 h/day exposure groups was approximately 10-15% COHb in rabbits and mice; COHb was not

28 followed in the 24 h exposure groups. The mice exposed to 7 h/day CO had a significant increase in the

29 number of resorbed pups (not seen in 24 h/day CO exposure). Fetal mouse weight was significantly

30 greater than control in the 7 h exposures and significantly less in the 24 h exposure groups with

31 corresponding significant differences in crown to rump length in the two groups. Rabbits seemed to be

32 less affected by CO exposure manifesting with no significant perinatal death or pregnancy loss.

33   Astrup et al. (1972) studied the effect of CO on fetal development after continuous CO exposure

34 (90 or 180 ppm CO) over the duration of gestation in rabbits. COHb was 16-18% and 8-9% in the 180

1   and 90 ppm exposure groups, respectively. In the immediate neonatal period, 24 h postpartum, 35%

2   (180 ppm) and 9.9% (90 ppm) of CO-exposed animals died. In the postpartum period after the first 24

3   hours and extending out to PND21, 90 ppm CO-exposed pups experienced 25% mortality versus 13% in

4   controls; there was no difference from control at the 180 ppm CO exposure level. Gestation length was

5   unchanged with CO exposure.

6   Fechter and Annau (1977) exposed Long-Evans rats in utero to 150 ppm CO continuously through

7   gestation (dam COHb 15%) and saw no effects of CO on litter mortality or pup number at PND1.

Maternal Diet

Maternal Protein Intake and Neonatal Mouse Mortality

8   Pregnant CD-1 mice were exposed intermittently (6 h/day for first two weeks of pregnancy) to CO

9   (0, 65, or 125 ppm) in combination with protein modified diets [27% (supplemental protein), 16%

10   (control), 8% (low), or 4% (very low protein)] to assess the role of CO exposure coupled with low-protein

11   diet on neonatal mortality at 1 week of age (Singh, 2006). Litter size was not affected by CO exposure.

12   Pup weight was inversely related to CO exposure and directly related to dam diet protein content during

13   pregnancy. Pup mortality at birth was directly related to CO exposure in certain protein groups

14   (supplemental, and 4% protein) and inversely related to the dam's dietary protein content. At 1 week of

15   age, pup mortality was significantly increased by CO-exposure. Dietary protein restriction also induced

16   pup mortality at 1 week of age; all pups in the 4% protein diet died by 1 week of age. CO exposure

17   (65 ppm only) combined with a normal protein diet significantly increased pup mortality at 1 week.

18   Animals receiving supplemental protein diets with CO exposure (65 and 125 ppm) had pups that had

19   significant increases in mortality at 1 week versus control air pups. Control protein diet pups had

20   significantly increased pup mortality at 1 week with CO exposure (65 ppm only) versus control air

21   animals (0 ppm CO). Contrary to other findings, low protein diet (8%) combined with CO (125 ppm) led

22   to a slight yet significant decrease in pup mortality at 1 week of age versus control (0 ppm CO). In

23   summary, these data show that in utero CO exposure induced increased neonatal mouse deaths at 1 week

24   in supplemental protein and normal protein diet exposure groups.

Maternal Low Protein Diet and CO-Dependent Teratogenicity

25   The role of diet as a contributor to teratogenicity of CO (0, 65, 125, or 250 ppm CO) in CD-1 mice

26   given a various protein diets (27%, 16%, 8% or 4% protein) during pregnancy was explored by Singh et

27   al. (1992). Timed pregnant CD-1 mice were exposed continuously to CO from GD8-GD18 of pregnancy

28   at which point animals were sacrificed and fetuses collected. Subsequent work by this group has shown

29   that low protein diets plus CO exposure act in an additive fashion to increase placental COHb in mice

30   (Singh et al., 1992; 2003). As expected, all levels of CO and the lowest protein diet (8 or 4% protein)

1 given to the dams during gestation resulted in significantly decreased fetal weight of normal fetuses at
2 GD18. CO exposure did not produce maternal toxicity except for a significant decrease in maternal
3 weight at GD18 with 4 and 8% protein diets versus control diet in non-CO-exposed animals. Dam dietary
4 protein levels were inversely related to gross malformations including jaw changes. All concentrations of
5 CO exposure significantly increased the percentage of litters with malformations. There was a CO dose-
6 dependent increase in percent of litters with malformations within each maternal dietary protein level.
7 Skeletal malformations were present in offspring with the percent of litters affected inversely related to
8 dietary protein levels. CO exposure concomitant with a low protein diet exacerbated the percent of
9 skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was
10 directly related to CO concentration and inversely related to maternal dietary protein levels. CO and
11 maternal dietary protein restriction had a synergistic effect on mouse offspring mortality and an additive
12 effect on malformations.

Zinc-Supplemented Protein-Deficient Maternal Diet and Mortality and Teratogenicity

13 Further studies by Neggers and Singh (2006) explored how teratogenicity and fetal mortality were
14 affected by zinc (Zn) modulation in CO-exposed pregnant dams (CD-1 mouse) given protein insufficient
15 diets. Developmental toxicitiy of CO was attenuated by protein supplementation, i.e., protein
16 supplemented animals (27%) showed a significantly lower incidence of fetal mortality versus 8% and
17 16% protein groups. Further, dietary restriction of both protein and Zn with co-exposure to CO during
18 gestation increased the incidence of pup mortality and malformations including gastroschisis.
19 Earlier studies by Schwetz et al. (1979) found fetal skeletal alterations in lumbar ribs or spurs were
20 significantly increased in the 7 h/day and 24 h/day gestationally CO-exposed fetal CF-1 mice collected
21 near term after CO exposure (250 ppm), over GD6-GD15 (dam gestational COHb 10-15% for 7 h/day
22 exposure, 24 h/day dam COHb not measured); these changes were not seen in similarly exposed fetal
23 rabbits (1979).
24 Astrup et al. (1972) studied the effect of CO exposure on fetal rabbit development via continuous
25 CO exposure (90 or 180 ppm with gestational dam COHb of 9% and 17%, respectively) over the duration
26 of gestation. Three pups (n = 123) in the 180 ppm CO group had deformities in their extremities at birth,
27 whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.

Skeletal Abnormalities

28 Earlier studies by Schwetz et al. (1979) found fetal skeletal alterations in lumbar ribs or spurs were
29 significantly increased in the 7 h/day and 24 h/day gestationally CO-exposed fetal CF-1 mice collected
30 near term after CO exposure (250 ppm), over GD6-GD15 (dam gestational COHb 10-15% for 7h/day
31 exposure, 24 h/day dam COHb not measured); these changes were not seen in similarly exposed fetal
32 rabbits.

1   Astrup et al. (1972) studied the effect of CO exposure on fetal rabbit development via continuous
2   CO exposure (90 or 180 ppm with gestational dam COHb of 9 and 17%, respectively) over the duration
3   of gestation. Three pups (n = 123) in the 180 ppm CO group had deformities in their extremities at birth,
4   whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.

Endogenous CO

Spontaneous Abortions

5   Idiopathic spontaneous abortions are more frequent in women with HO-1 polymorphisms in their
6   genome (Denschlag et al., 2004). To evaluate the role of HO-1 in spontaneous abortion, a mouse model
7   that spontaneously undergoes abortion (CBA/J x DBA/2J mice) (Zenclussen et al., 2006) was used with
8   and without HO adenovirus treatment to see if pregnancy outcome could be modulated by changing HO
9   concentration. HO-1 is known to protect organs from rejection (Kotsch et al., 2006) and thus, HO activity
10   may protect the developing fetus from rejection by the non-self maternal immune system. Pregnancy
11   outcome was significantly better (abortion rate significantly decreased) in mice overexpressing HO due to
12   adenovirus transfer. Thus, in this model, it appears that upregulation of the HO/CO system is able to
13   protect the developing fetus from spontaneous abortion.

Depressed Vascular Reactivity during Pregnancy and CO

14   CO through the production of soluble guanylate cyclase is able to stimulate the relaxation of
15   vascular smooth muscle (Villamor et al., 2000). Further, the role of HO expression is important in the
16   maintenance and outcome of pregnancy and lactation. During pregnancy, there is increased blood volume
17   without a concurrent increase in systemic BP; this is accomplished by a decrease in total peripheral
18   vascular resistance, to which CO contributes (Zhao et al., 2008). In humans, genetic polymorphisms in
19   HO-1 (microsatellite polymorphisms associated with altered HO-1 transcription) are linked to idiopathic
20   recurrent miscarriages (Denschlag et al., 2004) and administering HO-inhibitors to pregnant rodents
21   induced total litter loss (Alexandreanu and Lawson, 2002). Various pathologies of pregnancy including
22   IUGR and pre-eclampsia are associated with significant decreases in placental HO activity (Denschlag et
23   al., 2004; McLaughlin et al., 2003). Thus, the HO/CO system appears to be crucial in maintaining
24   pregnancy.

CO and Vasular Relaxation during Pregnancy

25   Isolated rat aortic rings and tail artery rings from pregnant dams (Sprague-Dawley rats) can be
26   relaxed by submersion in exogenous CO solutions (Longo et al., 1999). Further, the administration of the
27   HO inhibitor SnMP induced increased maternal BP (systolic, diastolic, and mean arterial pressure) during
28   pregnancy in FVB mice (Zhao et al., 2008). Zhao also showed pregnancy induced increased total body
29   CO excretion as measured in inhalation chambers, and that this increased CO production could be

1   significantly decreased by SnMP administration. Pregnant dam abdominal aortas (AA) are significantly

2   dilated with pregnancy and SnMP treatment leads to AA vasoconstriction to levels similar to non-

3   pregnant mice. Zhao looked at blood flow changes using Doppler technology and observed a significant

4   increase in uterine artery blood flow velocity following SnMP administration. Thus, it appears that the

5   increased CO production during pregnancy may partially account for the decreased peripheral vascular

6   resistance seen in pregnancy that prevents the increased blood volume of pregnancy from affecting BP.

Placenta

7   Women living at high altitude (chronic hypoxia exposure), women with pre-eclampsia, or women

8   who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant

9   decreases in HO-2 versus women living at lower altitude with uncomplicated pregnancies (Barber et al.,

10   2001; Lyall et al., 2000). FGR and pre-eclampsia HO-2 changes were detected in endothelial cells; HO-1

11   immunostaining was very low in the placenta. Women living at high altitude have an increased risk of

12   adverse pregnancy outcomes versus women living at lower altitudes (Zamudio et al., 1995). Oxygenation

13   is important in early pregnancy and triggers trophoblast invasion of the spiral arteries (Kingdom and

14   Kaufmann, 1997). Isolated human placenta exposed to solutions containing CO demonstrated a

15   concentration-dependent decrease in perfusion pressure (Bainbridge et al., 2002) further demonstrating

16   the role of CO in maintaining basal vasculature tone.

17   The endogenous generation of CO in the placenta has been demonstrated in chorionic villi of term

18   placenta (McLaughlin et al., 2001) with HO activity highest in the placenta near term (McLean et al.,

19   2000). CO can be generated from multiple endogenous sources; the source of CO in term human placental

20   chorionic villi was found to be the catalysis of heme by HO and not endogenous lipid peroxidation

21   (Ahmed et al., 2005). Term human placental cell types including syncytiotrophoblasts and

22   cytotrophoblasts were grown in cell culture under basal and hypoxic conditions to explore changes in HO

23   expression (Newby et al., 2005). HO-1 was expressed at significantly lower amounts in

24   syncytiotrophoblasts versus cytrotrophoblasts at normoxic conditions. HO-1 was unchanged in

25   cytotrophoblasts under hypoxia, but HO-1 was significantly decreased in hypoxic syncytiotrophoblasts.

26   HO-2 was unchanged in either cell type with hypoxia. These cell culture data can give insight into what

27   cell types might be responsive to hypoxia through the HO/CO system in the human placenta. Nonetheless,

28   these data should be interpreted remembering that isolated cell culture models lack the interaction with

29   the intact placenta and may lead to different physiological outcomes.

Uterus at Parturition

30   The addition of exogenous CO to isolated human and rat uterine tissue during pregnancy failed to

31   induce relaxation of uterine tissue (Longo et al., 1999). Thus, exogenous CO failed to quiet the

32   spontaneous contractility of rat or human myometrium (uterine smooth muscle). CO is not able to relax

1   all types of vascular smooth muscle (Brian et al., 1994), and pregnancy appears to modulate the response

2   of tissues to CO (Katoue et al., 2005).

3   HO-1 induction and HO concentration have been shown to be regulated by estrogen in the rat

4   (Sprague Dawley) uterus (Cella et al., 2006) during pregnancy and in non-gravid rats. This agrees with

5   work by Tschugguel et al. (2001) in which CO was generated by primary endothelial cells from human

6   umbilical veins and uterine arteries after exogenous 17-β estradiol administration.

Ovaries

7   **Ovarian Follicular Atresia.** As a part of normal follicular maturation in the ovaries, the majority of

8   follicles undergo artresia via apoptosis prior to ovulation. Harada et al. (2004) harvested porcine

9   granulosa cells from ovaries and found that cells naturally undergoing atresia or cell death more strongly

10   expressed HO-1 than did successful follicles. Addition of the HO substrate hemin or the HO inhibitor Zn

11   protoporphyrin IX (ZnPP IX) significantly induced or inhibited granulosa cell apoptosis, respectively. In

12   this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular

13   maturation.

14   **Ovarian Steroidogenesis.** HO-1 and HO-2 are localized in the ovaries in rats (Sprague Dawley)

15   and treatment of rat ovaries in vitro with CrMP, an inhibitor of HO, or with hemin, a substrate for HO

16   induced steroidogenic changes in the ovaries (Alexandreanu and Lawson, 2002). CrMP significantly

17   decreased ovarian production of gonadotrophin-induced androstenedione and progesterone without

18   affecting estradiol levels. Hemin treatment caused androstenedione and estradiol production from rat

19   ovaries in vitro. Thus, the HO/CO pathway may play an important role in rat ovarian steroidogenesis.

Anterior Pituitary and Heme Oxygenase

20   HO-1 and HO-2 are expressed in rat (Sprague Dawley) anterior pituitary and the secretion of

21   gonadotropins and prolactin is affected by HO inhibitors and HO substrates (Alexandreanu and Lawson,

22   2003a). The estrogen-induced afternoon surge of LH was advanced forward in time by chronic

23   administration of the HO inhibitor CrMP and this advance could be reversed by concomitant

24   administration of hemin, a HO substrate. The serum FSH surge was unaffected by CrMP or hemin but in

25   vitro treatment of GnRH-stimulated pituitaries with hemin led to a significant increase in FSH release.

26   The estrogen-dependent afternoon prolactin surge was inhibited or delayed by CrMP and CrMP+hemin

27   and CrMP significantly decreased prolactin release. In vitro studies using pituitary explants showed that

28   LH release was significantly increased by CrMP administration and unaffected by hemin. Modulation of

29   the HO/CO system in the anterior pituitary of the female rat led to altered secretion of gonadotropins and

30   prolactin.

Lactation and Pregnancy and HO Modulation

1   The role of the HO/CO system in estrous cyclicity, pregnancy, and lactation were monitored using

2   a Sprague Dawley rat model (Alexandreanu and Lawson, 2002). Pregnancy outcomes used dams that

3   were injected daily (GD5-GD16) with hemin, a HO substrate, or CrMP, a HO inhibitor that were followed

4   until 2-days post-term at which point they were euthanized and uteri examined for implantation sites and

5   fetuses. Another group of female rats were monitored for estrous cycle changes after receiving daily

6   hemin (10 or 11 days of injections) or CrMP (11 or 14 days of injections). A third group of animals was

7   monitored during lactation after receiving either CrMP or hemin exclusively during lactation (lactation

8   days LD5-LD15); the lactational effect was monitored by weighing pups out to weaning (LD21). Hemin

9   had no effect on any of the outcomes in this study, except a slight effect on litter weight gain during

10   lactational exposure. CrMP decreased time in estrous in a dose-dependent manner. CrMP exposure

11   significantly increased uterine fetal resorptions and led to no live births, possibly due to vasoconstriction

12   and associated ischemia of the placental vascular bed. CrMP induced decreased litter weight gain during

13   lactation, which the authors attributed to decreased maternal milk production or ejection problems as

14   cross-fostered pups regained weight lost during nursing on CrMP dams. The lactational effects seen in

15   this model may be explained by changes in prolactin as previously reported (Alexandreanu and Lawson,

16   2002). These data indicate that the HO/CO pathway is important in estrous cyclicity, parturition, and

17   lactation. Nonetheless, CrMP may also inhibit NO$^\bullet$ production, a mechanism that is distinct from

18   CO-dependent effects.

Summary of Toxicological Studies on Birth Outcomes

19   Endogenous CO production by various organs and the vascular system during pregnancy is

20   important for maintaining pregnancy and for the proper development of the fetus and/or offspring

21   postnatally. Exogenous CO addition has been shown to alter perinatal effects and birth outcomes in

22   various toxicological studies. Endogenous CO production is required for maintenance of a pregnancy as

23   has been shown by use of HO inhibitors; further, genetic polymorphisms in HO-1, which are associated

24   with increased HO expression upon stress, are associated with idiopathic recurrent miscarriages in a study

25   of a Caucasian population. A rodent study of spontaneous abortion demonstrated better pregnancy

26   outcome in animals in which HO-1 levels were increased by adenovirus transfer.

27   Rodent studies have explored the role of exogenous CO exposure on birth outcomes. Exogenous

28   CO exposure to rodent fetuses in utero significantly increased postnatal mortality. CO exposure in utero

29   induced teratogenicity in offspring in a dose-dependent manner that was further exacerbated by dietary

30   protein restriction or zinc depletion. Two studies noted skeletal abnormalities following in utero CO

31   exposure (180-250 ppm).

32   CO induces cGMP production by vascular smooth muscle beds, which can regulate vascular tone.

33   Thus, endogenous CO production is associated with maintenance of decreased peripheral vascular

1   resistance during pregnancy that prevents the increased blood volume of pregnancy from affecting BP.

2   This has been demonstrated in the human placenta and cells from the placenta with exogenous CO

3   addition further decreasing perfusion pressure. However, exogenous CO addition to human and rat uterine

4   tissue during pregnancy was unable to relax spontaneous myometrial contraction.

5   Estrogens have been shown to upregulate HO-1 levels in the uterus in non-gravid and pregnant rat

6   uteri; other studies have shown isolated cell culture systems administered 17-beta estradiol can generate

7   CO. In the female reproductive tract, the endogenous HO/CO system is involved in proper follicular

8   maturation, ovarian steroidogenesis, the secretion of gonadotropin and prolactin by the anterior pituitary,

9   in maintenance of lactation, and estrous cyclicity in rodent studies.

5.4.2.2. Developmental Effects

CNS Developmental Effects

Behavioral

10   **Active Avoidance Behavior.** To assess behavioral changes after in utero exposure, pregnant Wistar

11   rats were exposed to CO (0, 75 or 150 ppm) continuously over GD0-GD20 (De Salvia et al., 1995). Male

12   pups from exposed dams were evaluated for active avoidance behavior (mild shock avoidance) during

13   acquisition and reacquisition. This work was designed to expand on the studies of Mactutus and Fechter

14   (1985), who showed delayed acquisition (120 days of age) of an active avoidance task and disruption of

15   retention at a later test date (360 days) after continuous in utero CO exposure (150 ppm CO, dam COHb

16   concentrations of $15.6 \pm 1.1\%$), and to determine if these behavioral changes were permanent. De Salvia

17   et al. (1995) found there were no significant behavioral impairments in the low dose animals (75 ppm).

18   Animals exposed to the higher dose of CO (150 ppm) in utero had significantly impaired acquisition (at

19   3 and 18 months of age) and reacquisition (at 18 months of age) of conditioned avoidance behavior. The

20   authors speculated that this CO-dependent behavioral change may be mediated through neurotransmitter

21   signaling, specifically changes in dopamine in the neostriatum or nucleus accumbens. These studies

22   demonstrate that low level CO exposure in utero can lead to permanent behavioral changes in male

23   offspring.

24   Mactutus and Fechter (1984) also found that acquisition in a two-way conditioned avoidance

25   (flashing light warnings followed by mild footshock) test failed to improve with age of in utero

26   CO-exposed (150 ppm, dam COHb 15%) Long-Evans rats (male and female offspring) in contrast to

27   air-exposed controls who improved with age/maturation, indicating a failure in the associative process of

28   learning. They also found impairments in reacquisition performance, an index of retention, in PND31 rats

29   that had received continuous in utero CO exposure. Prenatal CO exposure induced learning and memory

30   deficits in male and female offspring.

1 **Habituation and Non-Spatial Working Memory**. Investigators have used animal models to study

2 how low dose CO exposure (75 or 150 ppm) during gestation can affect behavioral outcomes

3 (habituation, exploration of novel objects, and motor activity) in offspring as adults. Giustino et al. (1999)

4 exposed primparious pregnant Wistar rats to CO (0, 75 or 150 ppm) by inhalation from GD0-GD20.

5 Blood COHb concentrations (mean % ± SEM) on GD20 have been reported (0 ppm: 1.6 ± 0.1; CO

6 75 ppm: 7.36 ± 0.2; CO 150 ppm: 16.1 ± 0.9). At age 40 weeks, male offspring were given two trials. In

7 the first trial (T1), two similar objects were presented. In the second trial (T2), one object from the first

8 trial was presented as well as one novel object. Exploration time was defined as time exploring objects

9 during each trial. Global habituation was quantified as a comparison of the time spent exploring the two

10 objects in T1 to time spent exploring objects in T2. Discrimination between new and familiar objects was

11 measured in T2 by contrasting the time spent exploring the familiar object to time spent exploring the

12 new object. This object recognition tests for the preference that rats have for investigating novel objects in

13 lieu of familiar objects and is a measurement of non-spatial working memory. The results of this study

14 showed gestationally CO (75 and 150 ppm) exposed animals at 40 days of age have a significantly

15 decreased T1 during exploration of novel objects. Global habituation of control and 75 ppm CO rats

16 showed exploratory times with T2 <T1. However, T1 and T2 were not significantly different in the

17 150 ppm CO group, showing a lack of habituation after the second exposure to a previously viewed

18 object. Also, the decreased time spent with a familiar object by control rats was not seen in CO-exposed

19 animals (75 or 150 ppm). Further, the authors speculated that the mesolimbic dopaminergic system may

20 be responsible for these changes, possibly involving the nucleus accumbens. The human literature shows

21 a possible connection with these CO-dependent rodent effects; infants whose mothers smoked during

22 pregnancy manifest with habituation defects. Nonentheless, CO is just one of many consitutients of

23 cigarette smoke. The results from these animal toxicology studies showed that in utero exposure to CO

24 affects non-spatial working memory in young adult male rats.

25 **Long-Term Potentiation and Spatial Learning.** The above study agreed with earlier work showing

26 that hippocampal long-term potentiation (LTP) (Zhuo et al., 1993) of brain sections was significantly

27 affected by CO exposure with ZnPPIX, a HO inhibitor, blocking hippocampal LTP, but was in contrast to

28 Bing et al. (1995) who showed enhanced spatial learning in the Morris water maze in rodents exposed to

29 the HO inhibitor tin protoporphyrin (Sn-PP). Thus, distinct types of learning may be differentially

30 regulated by CO exposure, and endogenous CO, as modulated with the above inhibitors, may manifest

31 with different outcomes versus exogenous CO.

32 **Homing Behavior.** Development of homing behavior, orientation by the rat toward its home cage,

33 was significantly delayed in rats prenataly exposed continuously to 150 ppm CO (150 ppm) (Fechter and

34 Annau, 1980).

35 **Locomotor Effects.** Fechter and Annau (1977) exposed Long-Evans rats in utero to 150 ppm CO

36 continuously through gestation (dam COHb 15%) and saw significant effects of CO on pup locomotor

1   activity at PND1 and PND4 (both after subcutaneous L-DOPA administration to induce movement) and at
2   PND14, but not at PND21. CO-exposed pups showed significantly less activity than air-exposed controls
3   through the pre-weaning window.

4   Fechter and Annau (1980) exposed rats to CO (150 ppm) continuously throughout gestation and
5   found that exposed offspring manifested with poorer than normal performance on the negative geotaxis, a
6   reflexive response that results in a directional movement with or against gravity. In these studies, negative
7   geotaxis was defined as performing a 180° turn to face the top of an inclined plane. Continuous prenatal
8   CO exposure (125 ppm, GD7-GD18) in CD-1 mice impaired negative geotaxis at PND10 in a study by
9   Singh (1986). The standardization and use of geotaxis as a vestibular, motor or postural metric in infant
10 rodents has been debated in the literature (Kreider and Blumberg, 2005).

11   Prenatal exposure to CO (125 ppm, GD7-GD18) significantly affected the righting reflex (the
12 turning of an animal from its supine position to its feet) in exposed CD-1 mice on PND1. Also, the aerial
13 righting score, or turning 180° and landing on the feet when dropped from the supine position at a height,
14 was significantly decreased in pups exposed to CO in utero (65 and 125 ppm) (Singh, 1986) at PND14.
15 These behavioral tests indicated neuromuscular, vestibular or postural effects in the CO-exposed neonate.
16 Earlier studies by Fechter and Annau (1977) identified an early window of sensitivity for CO-dependent
17 motor activity defects of PND1-PND4, with recovery by PND21. Carratu's (2000) PND40 and PND90
18 monitoring of motor activity of in utero CO-exposed animals may be too late to detect CO-dependent
19 changes.

Neuronal

20   **Sciatic Nerve Myelination.** In utero exposure (GD0-GD20) to low levels of CO (0, 75 or 100 ppm)
21 and its effect on sciatic nerve myelination in male offspring was studied in Wistar rats (Carratù et al.,
22 2000). The dam CO blood concentration expressed as %COHb was determined for 0 ppm (GD10: $0.97 \pm$
23 0.02; GD20: 1.62 ± 0.1.), 75 ppm (GD10: 7.20 ± 0.12; GD20: 7.43 ± 0.62), 150 ppm (GD10: $14.42 \pm$
24 0.52; GD20: 16.08 ± 0.88). There were significant increases in %COHb in all CO-exposed animals. The
25 myelin sheath thickness of the nerve fibers was significantly decreased in CO-exposed animals (75 and
26 150 ppm). Axon diameter was not affected by CO exposure. Even though CO affected myelination, it did
27 not significantly affect motor activity of CO-exposed mice at 40 and 90 days. In conclusion, in utero
28 exposure of male rats to CO induces decreased myelination of the sciatic nerve without concomitant
29 decreases in motor activity.

30   **Brain and Peripheral Nervous System Myelination.** The effect of in utero exposure (GD0-GD20)
31 of Wistar rats to CO (0 or 150 ppm) on pup neuronal myelination was studied in the peripheral nervous
32 system and the brain of male offspring at 90 days of age (Carratù et al., 2000). CO exposure during
33 development induces hypoxia, and hypoxia can induce sphingomyelin changes which could lead to
34 impaired myelination and motor activity decrements. This study reported maternal COHb (mean % $\pm$

1   SEM) as 1.9 ± 0.04 and 16.02 ± 0.98 in control and 150 ppm CO-exposed animals, respectively. Prenatal

2   CO exposure had no effect on brain sphinganine (SA) or sphingosine (SO) levels in male offspring at

3   90 days of age. However, the sciatic nerve had significant increases in SO after CO exposure, no changes

4   in SA and a significant decrease in the SA/SO ratio at 90 days of age. Motor activity, which could be

5   affected by changes in myelination, showed no differences between CO and control animals at 90 days of

6   age. SO is an intermediate in sphingolipid turnover and SA is an intermediate of de novo sphingolipid

7   biosynthesis. These results demonstrate that sphingolipid homeostasis in the PNS but not CNS is

8   interrupted in offspring exposed in utero to CO without a manifestation of changes in motor activity.

Neurotransmitter Changes

9   **Medullar Cholinergic and Catecholaminergic Changes after In Utero CO Exposure and SIDS.**

10   One theory related to Sudden Infant Death Syndrome (SIDS) relates to aberrant development of brain

11   stem nuclei controlling respiratory, cardiovascular, and arousal activity. To address these changes in an

12   animal model, Tolcos et al. (2000a) exposed pregnant guinea pigs to CO (0 or 200 ppm) for 10 hours per

13   day over the last 60% of gestation leading to fetal and maternal COHb levels of 13% (versus control of

14   0.25%) and 8.5% (versus control of 1.6%), respectively. Guinea pigs are a good model because they

15   display a similar time course of CNS development to humans with the majority of development occurring

16   in utero. Pups and sows were collected near term and CO-exposed pups were found to have significant

17   decrements in body, brain, and liver weights as well as decreased crown to rump length when compared

18   to control pups. Medullar volume was also significantly decreased in CO-exposed pups. Neurotransmitter

19   systems were affected after CO exposure. Specifically, the catecholaminergic system of the brainstem

20   displayed significant decreases in immunoreactivity for tyrosine hydroxylase (TH), which is likely due to

21   decreased cell number in specific medullar regions. This was consistent with earlier work showing

22   aberrant respiratory responses (to asphyxia and CO_2) of offspring with prenatal CO exposure (McGregor

23   et al., 1998). The cholinergic system is also affected by prenatal CO exposure with significant increases in

24   choline acetyl-transferase (ChAT) immunoreactivity of the medulla and no changes in muscarinic

25   acetylcholine receptor. This is in contrast to human infants with SIDS that show decreased brainstem

26   muscarinic receptor binding (Kinney et al., 1995). ChAT changes in this study (Tolcos et al., 2000a) were

27   from areas of the medulla associated with tongue innervation, which is crucial to swallowing and which

28   may be impaired in SIDS infants.

29   **Mesolimbic Dopaminergic Effects and Impaired Sexual Behavior.** Exposure (GD0-GD20) of

30   pregnant Wistar rats to CO (0, 75 or 150 ppm) and its effects on adult (5 and 10 months of age) male

31   offspring sexual behavior and mesolimbic dopaminergic function was accessed by Cagiano et al. (1998).

32   Maternal COHb at GD10 was 1, 7, and 15% (0, 75 and 150 pm CO, respectively) and at GD20 was 1.5, 7,

33   and 16% (0, 75, 150 ppm CO, respectively). Using the aforementioned parameters, only animals at the

34   150 ppm CO exposure were significantly affected by CO exposure. At 5 months of age, CO-exposed male

1   offspring showed decrements in sexual behavior including an increase in mount to intromission latency, a

2   decrease in mount to intromission frequency, and a decrease in ejaculation frequency. Further,

3   administration of amphetamine, which stimulates copulatory activity, did not change CO-induced

4   increases in mount to intromission latency or decreases in mount to intromission frequency. Basal

5   extracellular dopamine concentration in the nucleus accumbens was unchanged after CO exposure.

6   However, when stimulated with amphetamine administration, control rats had increased release of

7   dopamine that was absent with CO-exposed rats. This demasculination of the CO-exposed offspring

8   paralleled earlier studies of mice exposed gestationally to hypoxia (Hermans et al., 1993). When rats were

9   followed at ten months of age, there were no significant changes in copulatory activity or neurochemical

10 parameters of the CO-exposed male offspring showing a recovery from earlier decrements. In summary,

11 in utero exposure to CO induced impairment of copulatory sexual behavior in male offspring with

12 accompanying changes in the mesolimbic dopaminergic system at five months of age. By ten months of

13 age, these changes were no longer detectable in CO-exposed males.

14   **Dopamine in the Neostriatum Is Affected by In Utero Plus Perinatal CO Exposure.** Exposure of

15 Long Evans rat dams and pups continuously to CO (75, 150, or 300 ppm with maternal COHb of 11, 19,

16 and 27%, respectively) from conception to PND10 induced significant elevations in dopamine in the

17 striatum at PND21 in CO-exposed offspring versus air exposed controls (Fechter et al., 1987).

18   **Cerebellum Weight and Neurotransmitter Changes after In Utero and Perinatal CO Exposure.**

19 Long Evans dams and pups exposed to CO (75, 150, or 300 ppm with COHb 9%, 15% and 24%) over the

20 duration of gestation and out to PND10, during the period of cerebellular development in the rat which is

21 equivalent to the in utero cerebellar development in the human, yielded a dose-dependent reduction in

22 cerebellum wet weight (significant at 150 and 300 ppm) at PND21 with increases in norepinephrine (NE)

23 concentration in the extrinsic noradrenergic system (a system that terminates in the cerebellum) in

24 CO-exposed animals monitored from PND14 to PND42, which is in contrast to a lack of NE change seen

25 in the cerebral cortex with in utero only CO exposure (Storm and Fechter, 1985a, b). With the same

26 exposures as Storm and Fechter, CO-exposed (300 ppm only) pups at PND21 had significant decreases in

27 cerebellar GABA content, decreased uptake of exogenous radio-labeled GABA, decreased fissures in the

28 cerebellum and decreased cerebellum size (Storm and Fechter, 1985b). Thus, in these studies, it appeared

29 that the cerebellum and neurotransmitters of the cerebellum were significantly affected by CO exposure

30 during cerebellar development.

31   **Neonatal Hyperthermia Effects on Neurotransmitters and Neuroglia.** To explore the interaction

32 of hyperthemia and hypoxia (CO-induced), two risk factors for SIDS, pregnant guinea pigs were exposed

33 to CO (0 or 200 ppm) for 10 h/day for the last 60% of gestation. At PND4 male pups were exposed to

34 hyperthermia or ambient temperature as a control. Brains were then collected at 1 and 8 weeks of age. CO

35 exposure had no effect on litter size or litter birth weight. In utero CO exposure sensitized some areas of

36 the brain to future hyperthermic insults. Specifically, CO plus hyperthermia induced significant increases

1 in serotonin in multiple brain regions (NTS, DMV, and hypoglossal nucleus) at 1 week of age; this change

2 was no longer evident at 8 weeks of age. Hyperthermia exposure alone induced decreased met-enkephalin

3 neurotransmitter immunoreactivity at 1 week of age that was absent at 8 weeks and absent in CO plus

4 hyperthermia exposed animals. Brain stem neurotransmitter (met-enkephalin, serotonin, TH, substance P)

5 immunohistochemical differences were not apparent with CO treatment alone. At 8 weeks of age, CO

6 plus hyperthermia exposure induced glial aggregations and gliosis surrounding infarct or necrotic areas in

7 the brain and the medulla lesions stained positive for glial fibrillary acidic protein (GFAP). GFAP

8 upregulation is classically seen with neuronal diseases or following neurodegeneration. Gross structural

9 observations revealed no differences in the medulla or cerebellum following in utero CO exposure alone.

10 Together, these data showed that CO exposure in utero sensitizes the brain to future hyperthermic insults

11 leading to generation of necrotic lesions in the brain and changes in neurotransmitter levels.

12 **Glutamatergic Transmission Impairment by In Utero CO Exposure.** Pregnant Wistar rats were

13 exposed continuously to CO (75 ppm) during gestation (GD5-GD20) (Antonelli et al., 2006). Primary cell

14 cultures obtained from the cerebral cortex of exposed offspring (PND1) had decreased extracellular

15 glutamate (basal and K^+-evoked) levels versus air exposed controls, which may functionally impair

16 cortical glutamatergic transmission in CO-exposed offspring, possibly affecting learning and memory.

Electrophysiological Changes

17 Gestational exposure of pregnant Wistar rats to continuous CO (0, 75 or 150 ppm with dam COHb

18 for 150 ppm CO of 15%) for the entirety of gestation yielded electrophysiological changes in the

19 peripheral nervous system with reversible changes (present at PND40 and absent at PND270) in sodium

20 channel inactivation kinetics and irreversible changes in the sodium equilibrium potential (Carratu et al.,

21 1993) in CO-exposed pups (75 and 150 ppm) versus control pups. These voltage clamp studies showed

22 that in utero CO exposure had both reversible and irreversible effects on sodium channels, which are

23 essential for proper electrophysiological function of the PNS.

The Developing Auditory System

24 The developing auditory system of rodents has recently been recognized to be a target of CO

25 exposure. Low concentrations of CO exposure via inhalation (0, 12.5, 25, or 50 ppm) over PND8-PND22

26 during the period of extensive auditory development and synaptogenesis was studied by Webber , who

27 looked specifically at the inferior colliculus (IC), an auditory integrative section of the midbrain. Rodent

28 pups were allowed to be maternally reared (MR) or were removed from their respective dams and

29 nutritionally supported with gastronomy-reared nutrition (AR), an artificial feeding system or received

30 AR plus CO exposure (ARCO). AR reared pups were fed a milk substitute comparable to natural rat milk

31 via intragastric cannulation. AR allowed nursing pups to be exposed to CO without possible

32 CO-dependent developmental changes being confounded by materal CO co-exposure or lactational

1   exposures. Half of the pups were collected at PND27 and half were collected at PND75-PND77. Brains

2   were sectioned and stained for c-Fos, a marker of neuronal activation in the nervous system. AR and MR

3   exposed animals were found to have no significant differences in c-FOS staining. Further, c-Fos

4   immunoreactivity in the central IC was significantly decreased in the ARCO-exposed animals at both

5   PND27 and PND75-PND77 over all dose groups (12.5, 25, or 50 ppm CO); immnunostaining of other

6   subregions of the IC were not affected by CO. These studies showed exposure to low concentrations of

7   CO during development can lead to permanent changes in the auditory system of mice that persist into

8   adulthood.

9   Others have shown that mild CO exposure early in development impacts cochlear development

10   (Lopez et al., 2003). Sprague Dawley rats were reared from PND6 to weaning (PND19-PND20) on milk

11   substitutes using gastronomy-feeding (AR) or maternally reared (MR). These pups were exposed to low

12   levels of CO (12 or 25 ppm, ARCO) via inhalation from PND6-PND27. At PND27, the animals were

13   sacrificed and examinations of the cochlea were performed to determine the effect of mild CO exposure.

14   In ARCO animals, there was no evidence of damage to the inner or outer hair cells. After CO exposure

15   (25 ppm), there was atrophy or vacuolization of the nerve cells that innervate the inner (not outer) hair

16   cells. Also, fibers of the 8th cranial nerve at the level of the internal auditory canal of the ARCO animals

17   exposed to 25 ppm CO had distorted myelination and vacuolization of the axoplasm. Energy production

18   markers in the organ of corti and spiral ganglion neurons including cytochrome oxidase and NADH-TR

19   were significantly decreased in 25 but not 12 ppm CO exposure groups versus control (AR and MR).

20   Expression of the calcium-mediated myosin ATPase in the organ of corti and spiral ganglion neurons was

21   significantly decreased in the 25 ppm CO exposure group when compared to controls. Together, these

22   findings show that specific areas of the cochlea were affected after low level developmental CO exposure.

23   Two non-invasive measurements of auditory function, otoacoustic emissions testing (OAE) and

24   auditory brainstem response (ABR) are routinely performed on the majority of human newborns in

25   hospitals throughout the U.S. to detect early hearing loss. OAE requires the insertion of a microphone and

26   earphone into a sleeping newborn's ear; when a sound is generated, an echo is recorded on the

27   microphone in a functional ear and absent or reduced in an affected ear. The ABR measures brainwaves

28   generated after exposure to a sound. Otherwise healthy, term human infants born to smoking mothers

29   have impaired cochlear development, albeit mild, with decreased amplitudes of transient evoked

30   otoacoustic emissions versus newborns born to non-smokers (Korres et al., 2007); CO is one of many

31   potential affective components of cigarette smoke.

32   Stockard-Sullivan et al. (2003) used these two functional tests in Sprague-Dawley rat pups

33   receiving ARCO (12, 25, or 50 ppm CO) to determine how continuous (22 h/day) perinatal CO exposure

34   (PND6-PND22) functionally affected hearing in the developing rat. OAEs were measured in two ARCO

35   groups (25 and 50 ppm) at PND22. At 50 ppm, significant reductions in OAE amplitude were detected at

36   specific frequencies (7.13 and 8.01 kHz). ABR conduction time was not affected in CO-exposed animals

1 (12, 25, 50, 100 ppm). Using another otoacoustic test revealed significant attenuation of the action

2 potential of the 8th cranial nerve with ARCO exposure (12, 25, and 50 ppm CO) versus AR controls at

3 PND22, but this is complicated by the finding that AR control animals had significant attenuation of the

4 8th cranial nerve AP versus MR control animals, implying that artificial diet contributes to AP changes

5 before CO was introduced. Nonetheless, the ARCO-dependent attenuation of the 8th cranial nerve AP

6 (versus AR control) was permanent, persisting until adulthood in the 50 ppm CO exposure group (the

7 only CO group monitored); OAE was not measured in adult animals. These functional tests reported that

8 neonatal exposure to low concentrations of CO can induce auditory functional changes in rodents.

9   Multiple high dose CO studies have shown a role for ROS in CO-dependent ototoxicity. Studies

10 using high dose CO (i.p. injection of pure CO [35 mL/kg] inducing 40% COHb) have shown

11 CO-dependent otoxoxicity in adult guinea pigs as measured by loss of threshold of cochlear compound

12 action potentials (CAP) could be attenuated using the free radical inhibitors PBN (a spin trap) or

13 allopurinol (a superoxide scavenger), implicating ROS in high dose CO dependent cochlear damage

14 (Fechter et al., 1997). Fechter et al. (2002) found that noise-induced hearing loss (NIHL) was potentiated

15 by CO (500 ppm) coexposure. In the same manuscript, Fechter et al. (2002) showed potentiation of NIHL

16 post-CO exposure (1,200 ppm for 30 minutes in adult rodents) with significant elevations seen in free

17 radical production above control animals only in the CO+NIHL group; an interesting finding of this study

18 was that the acute high dose CO exposure did not induce significant increases in free radical generation

19 with this high dose acute CO exposure alone. A possible mechanism for this high-dose CO cochlear

20 damage is via glutamate release. Use of an NMDA inhibitor attenuated acute CO-dependent (1,200 ppm

21 or i.p. injection of pure CO [35 mL/kg]) CAP threshold disruption at 15 minutes post CO-exposure.

22 Glutamate is a known ROS generator (Liu and Fechter, 1995) . The glutamate receptor blockade did not

23 afford long-term protection (1 h or 4 weeks post-CO exposure) from high doses of CO (1,200 ppm or i.p.

24 injection of 35ml/kg pure CO) (Chen et al., 2001; Liu and Fechter, 1995)

25   Cognizant of the ROS-dependent contribution to the auditory changes seen with high dose

26 CO-exposure in animal toxicology models, Webber et al. investigated whether limiting iron availability

27 through dietary iron restriction could confer protection against low dose perinatal CO-dependent auditory

28 decrements. Briefly, rat pups were reared from PND6 through the duration of lacation with gastronomy-

29 reared nutrition with adequate iron (AR) or AR with iron-deficient diets (ARID) or pups were reared with

30 their respective dams (MR). Animals exposed to CO were denoted as ARCO and ARIDCO and received

31 either 25 or 100 ppm CO from PND9 to PND24 with all animals collected on PND27. ARID, ARIDCO,

32 and ARCO groups were compared to controls (MR and AR) to determine differences in the auditory

33 system after low iron exposure and/or CO exposure. Coincidentally, ARIDCO mice became anemic but

34 ARID mice were not. Cochlea were stained for transferrin, an iron-transport protein, and low iron

35 exposure (ARID and ARIDCO) induced increased transferrin. Neurofilament loss from the spiral

36 gangilian neurons and somas after ARCO treatment was rescued (no detectable neurofilament loss) with

1 low iron (ARIDCO); ARID treatment induced no change in neurofilaments. CuZn superoxide dismutase

2 (SOD1) was significantly increased with CO exposure (ARCO) and rescued in ARIDCO animals; SOD1

3 was unchanged in low iron only animals (ARID). Low iron treatment or CO exposure alone led to

4 significant decreases in c-fos positive cell numbers of the central IC, but c-fos levels were unchanged

5 after low iron diet concomitant with CO exposure (ARIDCO). These authors postulated that ROS

6 generated via the interaction of peroxide and iron (via the Fenton reaction or Haber Weiss chemistry) can

7 lead to an oxidative stress which leads to decreased c-fos expression in the IC and decreased numbers of

8 neurofilaments; decreasing the available iron to the developing animal decreases the total pool available

9 for ROS generation. Further, the attenuation of the elevated SOD levels with iron restriction post

10 CO-exposure gives credence to this model. The changes in c-fos are not completely explained as ARID

11 mice also show significant decreases in c-fos IC staining.

Summary of Toxicological Studies on Developmental Central Nervous System Effects

12   Toxicological studies employing rodent models have shown that low level CO exposure during the

13 in utero period can adversely affect adult outcomes including behavior, neuronal myelination,

14 neurotransmitter levels or function, and the auditory system. In utero CO exposure has been shown to

15 impair active avoidance behavior in male offspring after in utero CO exposure. Other studies have shown

16 that after in utero CO exposure, adult male offspring manifest with altered behavior including a lack of

17 habituation and an absence of familiarity with previously viewed objects (non-spatial memory). In two

18 separate studies, in utero CO exposure (75 and 150 ppm) was associated with significant PNS

19 myelination decrements without associated changes in motor activity in adult animals. With in utero CO

20 exposure peripheral myelination was decreased and the sphingolipid homeostasis (150 ppm CO) was

21 disrupted; CNS myelination was not affected. Multiple studies demonstrated that in utero CO exposure

22 affected glutamatergic (75 ppm), cholinergic (200 ppm), catecholaminergic (200 ppm), and dopaminergic

23 (75 ppm) neurotransmitter levels or transmission in exposed male rodents. Possible or demonstrated

24 adverse outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include

25 respiratory dysfunction (150 ppm), impaired sexual behavior (150 ppm), and an adverse response to

26 hyperthermic insults resulting in neuronal damage (200 ppm). Finally, in utero CO exposure has been

27 shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood.

28 The IC showed decreased c-Fos staining indicating decreased neuronal activation post-perinatal CO

29 exposure (12 and 25 ppm CO). The cochlea also showed adverse effects after in utero CO exposure with

30 atrophy of nerve cells innervating the inner hair cells (25 ppm CO), impaired myelination of the 8th

31 cranial nerve (25 ppm CO), and decreased energy production in the organ of corti (25 ppm CO). Auditory

32 functional testing using OAE (50 ppm CO) and attenuation of the 8th cranial nerve AP (12, 25, 50,

33 100 ppm CO) on rodents exposed perinataly to CO showed that CO-exposed nenonates had auditory

34 decrements at PND22 (OAE and AP) and into adulthood with AP decrements. Further studies limiting

1   iron consumption in the diet protected CO-exposed mice from cochlear damage at the spiral ganglion,

2   possibly through a diminuation of ROS. Together, these animal studies demonstrate that in utero or

3   perinatal exposure to CO can adversely affect adult behavior, neuronal myelination, neurotransmission,

4   and the auditory system in rodents.

Cardiovascular and Systemic Developmental Effects

Myocardial Electrophysiological Maturation

5   A rat model of in utero exposure was employed to study CO effects on the development of cardiac

6   myocytes. Results demonstrated that in utero CO exposure (150 ppm) alters postnatal cellular

7   electrophysiological maturation in the rat heart (Sartiani et al., 2004). Specifically, at 4 weeks of age, the

8   action potential duration (APD) of isolated cardiac myocytes from CO-exposed animals failed to shorten

9   or mature as did the APD of control animals. Further, the two ion conduction channels I_{to} (transient

10   outward current, K^+-mediated) and $I_{Ca,L}$ (L-type Ca^{2+} current), which largely control the rat APD, were

11   significantly different from control animals after in utero CO exposure, at 4 weeks of age. These

12   CO-dependent changes resolved by 8 weeks of age, reflecting a delayed maturation. The authors noted

13   that human SIDS is increased in infants whose mothers are smokers and cigarette smoke is composed of

14   approximately 4% CO. Further, these authors postulated that a CO-dependent delay in

15   electrophysiological maturation of the cardiac myocyte (lack of APD shortening) could lead to

16   arrhythmias and thus could be associated with SIDS deaths. However, no SIDS-like cardiac abberations

17   were followed in intact Holter-monitored rats in this study.

Heart Morphological changes after In Utero or Perinatal CO Exposure

18   Multiple authors have reported cardiomegaly following in utero low level CO exposure. Prigge and

19   Hochrainer (1977) reported increased fetal Wistar rat heart wet weight or cardiomegaly following

20   continuous in utero CO (60, 125, 250, and 500 ppm) exposure with no decreases in near term fetal

21   hematocrit or Hb levels seen at exposures below 250 ppm. Fechter et al (1980) found that prenatal

22   exposure to CO affected cardiac development in exposed offspring. Long Evans rats that were exposed to

23   CO continuously (150 ppm) during gestation manifested with significant elevations in wet heart weight at

24   PND1 as well as heart weight in relation to body weight; body weight was significantly decreased in

25   CO-exposed pups. At no other age measured (PND4, PND14, or PND21) did the CO-exposed pups show

26   increased heart weight (absolute or relative wet or dry weight) versus control. At PND14, control pups

27   that had significantly increased body weight, also had significantly increased absolute heart weights (dry

28   and wet) versus CO-exposed offspring. Dry to wet weight ratios revealed that the increased heart weight

29   of CO-exposed pups at birth was due to edema or water content. Penney et al. (1982) studied

30   CO-dependent (500 ppm) cardiomegaly in neonates (continuous CO exposure for 32 days starting at

1   PND1). Other studies of adult male Charles River derived rats exposed to CO for 6 weeks (at 400 or

2   500 ppm CO) as adults only developed CO-dependent cardiomegaly during exposure that significantly

3   regressed within a couple of months after termination of CO exposure (Styka and Penney, 1978).

Systemic Immune Toxicology after In Utero CO Exposure

4   In utero exposure (GD0-GD20) of male Wistar rats to relatively low CO (0, 75, or 150 ppm)

5   concentrations induced reversible changes in macrophage function (Giustino et al., 1993). The killing of

6   *Candida albicans* (yeast) by splenic macrophages was significantly decreased at PND15 in in utero

7   CO-exposed male offspring (75 and 150 ppm) but recovered and maintained function by PND21 and

8   PND60. Macrophage phagocytosis of *Candida albicans* was significantly reduced at PND15 and PND21

9   in CO-exposed males (150 ppm only) and recovery was seen at PND60. Superoxide production by the

10   splenic macrophage respiratory burst was significantly decreased at PND15 and PND21 after in utero CO

11   exposure (150 ppm only) with recovery to control levels at PND60. In summary, CO exposure in utero

12   leads to a reversible and dose dependent loss of function of splenic macrophages with decreased killing

13   ability, decreased phagocytosis, and decreased ROS production during the macrophage respiratory burst.

14   Further studies by the same laboratory showed that in utero exposure of male Wistar rats to CO

15   exposure induced changes in the frequency of splenic immunocompetent cells (Giustino et al., 1994).

16   Specifically, there was a significant decrease in the number of leucocyte common antigen cells (LCA+)

17   cells in PND21 male rats exposed during gestation to 150 ppm CO; other cell subpopulations including

18   macrophages, Major Histocompatibility (MHC) II cells, T and B lymphocytes did not show significant

19   decreases in cell numbers with with CO exposure.

Summary of Toxicological Studies of Cardiovascular and Systemic Development

20   In utero CO exposure is associated with various adverse, albeit non-persistent, cardiac aberrations.

21   Exposure to 150 ppm induced a delayed maturation of the cardiac action potential in CO-exposed

22   offspring. Specifically, APD failed to shorten at 4 weeks of age but shortened to control duration by 8

23   weeks of age. Also, ion channels in CO-exposed animals, which are related to APD, were significantly

24   different from controls at 4 weeks but matured to control levels by 8 weeks of age. In other studies,

25   continuous in utero CO exposure (60, 125, 250, and 500 ppm) induced cardiomegaly at PND1 which was

26   transient and regressed by PND4. Systemic immunocompromise was displayed in two studies focusing on

27   splenic cells. In the first study, a reversible and dose dependent loss of function of splenic macrophages

28   with decreased killing ability, decreased phagocytosis, and decreased ROS production during the

29   macrophage respiratory burst was observed (150 ppm but not 75 ppm CO). In the second study, the

30   distribution of splenic immunocompotent cells was skewed because of a decrease in the number of LCA+

31   cells in PND21 male rats exposed during gestation to 150 ppm CO. In conclusion, in utero exposure to

32   low doses of CO (60, 125, 150, 250, or 500 ppm) is able to induce transient changes in cardiac

1 morphology, cardiac action potentials, and systemic immunity that may make the immediate neonatal
2 period a time for a CO-exposed animal more susceptible to other outside stressors.

5.4.3. Summary of Birth Outcomes and Developmental Effects

3 The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for
4 PTB and cardiac birth defects. These outcomes were not addressed in the 2000 CO AQCD, which
5 included only two studies that examined the effect of ambient CO on LBW. Since then, a number of
6 studies have been conducted looking at varied outcomes, including PTB, birth defects, fetal growth
7 (including LBW), and infant mortality.
8 There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first
9 trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB
10 outcome were conducted in California, and these reported consistent results whereby all studies reported a
11 significant association with CO exposure during early pregnancy, and exposures were assigned from
12 monitors within close proximity of the mother's residential address. Additional studies conducted outside
13 of the U.S. provide supportive, though less consistent, evidence of an association between CO
14 concentration and PTB.
15 Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these
16 studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects.
17 This insult to the heart is coherent with results of human clinical studies demonstrating the heart as a
18 target for CO effects (Section 5.2). Animal toxicological studies provide additional evidence for such an
19 insult to the heart, and reported transient cardiomegaly at birth after continuous in utero CO exposure (60,
20 125, 250 and 500 ppm CO), delayed myocardial electrophysiolgical maturation (150 ppm CO), or
21 systemic splenic immunocompromise (75 or 150 ppm CO). Toxicological studies have also shown that
22 exogenous continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a
23 dose-dependent manner that was further exacerbated by dietary protein restriction (65 ppm CO) or zinc
24 depletion (500 ppm CO). Toxicological studies of exogenous CO exposure over the duration of gestation
25 have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in
26 prenatally exposed offspring.
27 There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal
28 growth in epidemiologic studies. In general, the reviewed studies, summarized in Figures 5-7 through 5-9,
29 reported small reductions in birth weight (ranging ~5-20 g). Several studies examined various
30 combinations of birth weight, LBW, and SGA/IUGR and inconsistent results are reported across these
31 metrics. It should be noted that having a measurable, even if small, change in a population is different
32 than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is

1 difficult to conclude if CO is related to a small change in birth weight in all births across the population,

2 or a marked effect in some subset of births.

3   In general, there is limited epidemiologic evidence that CO is associated with an increased risk of

4 infant mortality during the neonatal or post-neonatal periods. In support of this limited evidence, animal

5 toxicological studies do provide some evidence that exogenous CO exposure to pups in utero significantly

6 increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and

7 prenatal mortality (7 h/day, 250 ppm CO).

8   Evidence exists for additional developmental outcomes which have been examined in toxicological

9 studies, but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and

10 memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system.

11 Structural abberations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and

12 auditory related nerves (25 ppm CO) were seen in pups after neonatal CO exposure. Auditory functional

13 testing using OAE (50 ppm CO) and 8th cranial nerve AP amplitude measurements (12, 25, 50, 100 ppm

14 CO) on rodents exposed perinataly to CO showed that CO-exposed nenonates had auditory decrements at

15 PND22 (OAE and AP) and permanent changes into adulthood with AP (50 ppm CO).

16   Overall, there is limited, though positive, epidemiologic evidence for a CO-induced effect on PTB

17 and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and

18 infant mortality. Animal toxicological studies provide support and coherence for these effects. Both

19 hypoxic and non-hypoxic mechanisms that could lead to such effects have been proposed in the

20 toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying

21 reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for

22 some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these

23 associations in animal toxicological studies, **the evidence is suggestive of a causal relationship**

24 **between long-term exposures to relevant CO concentrations and developmental effects and birth**

25 **outcomes**.

5.5. Respiratory Effects

5.5.1. Epidemiologic Studies with Short-Term Exposure

5.5.1.1. Pulmonary Function, Respiratory Symptoms, and Medication Use

26   The 2000 CO AQCD briefly discussed the potential acute respiratory health effects associated with

27 short-term exposure to CO. An evaluation of the epidemiologic literature at the time did not find any

28 evidence of an association between short-term exposure to CO and lung function, respiratory symptoms,

1 or respiratory disease. As a result, the 2000 CO AQCD did not conclude that a causal association exists

2 between short-term exposure to CO and respiratory health effects. The following section evaluates the

3 current literature that examines the potential association between short-term exposure to CO and

4 respiratory health effects. Table 5-14 lists the studies evaluated in this section along with the respiratory

5 health outcomes examined and CO concentrations reported.

Table 5-14.   Range of CO concentrations reported in key respiratory morbidity studies that examined effects associated with short-term exposure to CO.

Author	Location	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Rabinovitch et al. (2004)	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)	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)[1]	The Netherlands n = 68	March - April[2]	Pulmonary function	24-h avg	0.80	Max: 1.34
Ranzi et al. (2004)[1]	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)[1]	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)[1]	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)[1]	Kuopio, Finland n = 33	2/1994-4/1994	Pulmonary function	24-h avg	0.52	Maximum: 2.43
Chen et al. (1999)	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)	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)	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)	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)	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

Author	Location	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
von Klot et al. (2002)[1]	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
Park et al. (2005a)	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)	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)[1]	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

[1] 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 tempterature.
[2] These studies did not provide the year(s) in which air quality data was collected.

Pulmonary Function

1   Rabinovitch et al. (2004) examined the association between exposure to ambient air pollutants and
2   asthma exacerbation in a panel of urban minority children, 6-12 years old, with moderate to severe asthma
3   over three winters in Denver, CO. The investigators examined pulmonary function by measuring forced
4   expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF) in the morning on school days, and
5   also at night on weekends or other nonschool days. Using a 3-day moving average (lag 0-2) for all
6   pollutants, Rabinovitch et al. (2004) did not find an association between CO and either lung function
7   parameter during the morning or at night.
8   Silkoff et al. (2005) also examined lung function in Denver during the winter months, but in a
9   panel of former smokers that were at least 40 years old and had been diagnosed with COPD. In this study
10 CO concentrations were similar to those reported in Rabinovitch et al. (2004). The authors examined the
11 association between exposure to air pollutants and lung function (i.e., FEV_1 and PEF) in both the morning
12 and the evening. Silkoff et al. (2005) found contradictory results when examining the effects of CO for
13 each of the winter periods separately, 1999-2000 and 2000-2001. During the analysis of the first winter
14 (i.e., 1999-2000) CO was not found to be associated with lung function decrements at any lag, but an
15 increase in FEV_1 during the morning was observed at lag 1. For the second winter (i.e., 2000-2001) the
16 authors found a significant negative association between CO exposure and FEV_1 in the evening at lag 2
17 (Figure 5-10). CO was not found to be associated with PEF at any lag during either winter period. Silkoff
18 et al. (2005) postulated that the difference in results for the two study periods could be due to higher
19 pollution concentrations along with somewhat lower temperatures and higher humidity in 2000-2001.
20 However, mean CO levels remained relatively constant between the first and second winters, whereas,
21 PM_{10}, $PM_{2.5}$, and NO_2 concentrations all increased. The decrements in FEV_1 observed in the second

1   winter, therefore, may have been due to the slightly worse, although not significantly different, baseline

2   lung function of the panel of subjects used during the second winter (Silkoff et al., 2005).
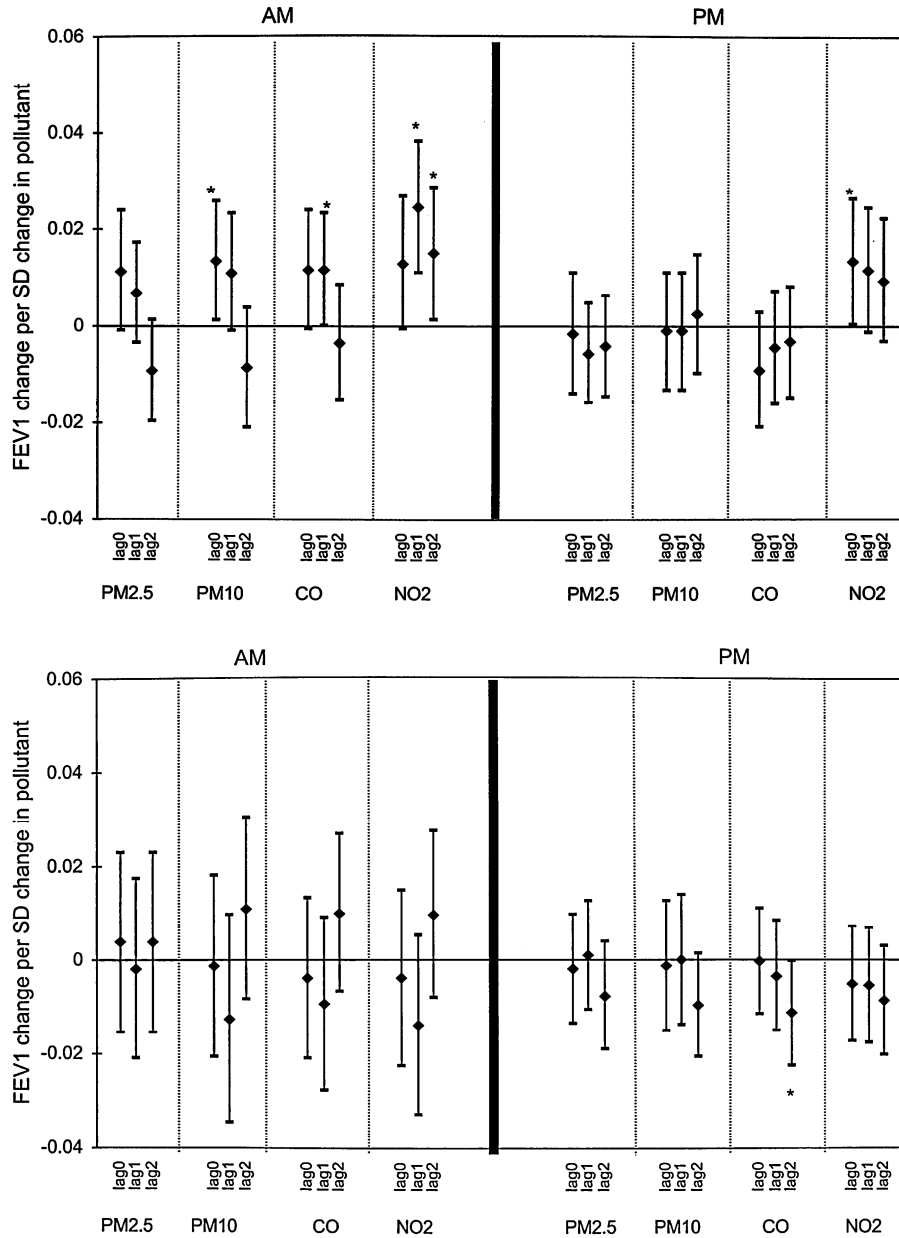
Figure 5-10.   **Estimates for FEV$_1$ change expressed per SD change of the individual pollutants PM$_{2.5}$, PM$_{10}$, CO, and NO$_2$ for the 1999-2000 (top) and 2000-2001 (bottom) winters at lags 0, 1, and 2. The asterisk indicates a significant association (p <0.05).**

1   In the recent literature, the majority of studies that examined the association between short-term

2   exposure to CO and lung function have been conducted in Europe. The results from these studies

3   contradict those reported in the U.S.-based studies previously discussed. Negative associations between

4   short-term exposure to CO and lung function were observed primarily in individuals with underlying

5   respiratory conditions; however, some evidence also exists for effects in children that live in urban

6   environments. Penttinen et al. (2001) examined the association between CO and lung function in a panel

7   consisting of 57 non-smoking adult asthmatics during the winter and spring in Helsinki, Finland. The

8   authors observed negative associations with PEF (L/min) for a 0.5 ppm increase in 24-h avg CO

9   concentrations in the morning at lag 1 (β = -0.54, SE = 0.084), and in the afternoon (β = -1.52, SE = 0.29)

10   and evening (β = -1.81, SE = 0.27) for a 5-day average. In two-pollutant models with daily mean particle

11   number concentration (PNC), CO effects on PEF in the morning were attenuated at lag 1, but remained

12   negative. In addition, negative associations with PEF persisted in the afternoon and evening in a two-

13   pollutant model at lag 0. In this study, high correlations between UFP and other traffic generated

14   pollutants (e.g., CO and NO_X) make it difficult to attribute the observed respiratory effects to a specific

15   pollutant.

16   Lagorio et al. (2006) also conducted a study that examined the association between CO and lung

17   function in adults. In this study, 3 panels of subjects that resided in Rome, Italy, were selected with

18   underlying asthma, COPD, or IHD. The ages of the subjects varied depending on the panel, but overall

19   the subjects ranged from 18-80 years old. In single-pollutant models CO was found to be negatively

20   associated with both FVC (forced vital capacity) and FEV_1 at most of the lags examined (i.e., 0, 0-1, and

21   0-2) for both the COPD and asthma panels. No association was observed between CO and FVC or FEV_1

22   in the IHD panel. Lagorio et al. (2006) did observe high correlations between CO and $PM_{2.5}$, but not NO_2.

23   Unfortunately, copollutant models were not conducted in this analysis to identify whether the CO

24   associations observed are confounded by other pollutants.

25   Timonen et al. (2002) examined the effect of CO on bronchial responsiveness and pulmonary

26   function (i.e., FVC, FEV_1, MMEF, and AEFV) in a panel of children 7-12 years old with chronic

27   respiratory symptoms during the winter in Kuopio, Finland. The authors found that CO was significantly

28   associated with decrements in baseline lung function for FVC (mL) at lags 2 (-17.5 mL), 3 (-24.8 mL),

29   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

30   concentration. However, CO was not associated with exercise induced changes in lung function. Overall,

31   Timonen et al. (2002) found that high concentrations of combustion byproducts (i.e., BS, PM_{10}, particle

32   numbers, NO_2, and CO) were associated with impairment in baseline lung function. These associations,

33   along with the high correlation between pollutants, contributed to the inability of the authors to conclude

34   that the lung function effects observed were due to biological changes in lung pathology specific to CO

35   exposure.

1   Chen et al. (1999) examined the effect of CO on lung function in a panel of 8-13 year old asthmatic

2   children in Taiwan. The authors observed an association between short-term exposure to CO and

3   decrements in FVC (mL) at a 2-day lag when using daytime average CO concentrations (from 0800 to

4   1800) in a single-pollutant model. In addition, the authors found a high correlation between CO and NO_2

5   concentrations (r = 0.86-0.98), but did not conduct multipollutant analyses to examine the effect of each

6   pollutant.

7   One additional study, Fischer et al. (2002), examined the association between CO and respiratory

8   health, specifically lung function in a non-selected cohort study of 68 children ages 10-11 that live in an

9   urban environment (i.e., Utrecht, the Netherlands). In this study, the authors examined whether eNO was

10   a more sensitive measure of lung damage than the traditional pulmonary function measurements

11   (i.e., FVC, FEV_1, PEF, and MMEF). Fischer et al. (2002) found negative associations between CO and

12   FEV_1, PEF, and MMEF at both lags 1 and 2. Additonally, the authors found an association between CO

13   and an increase in eNO at lag 1. However, the study did not present the correlations between pollutants or

14   examine copollutant models.

Respiratory Symptoms in Asthmatic Individuals

15   Upon evaluating the literature that examined the association between short-term exposure to CO

16   and respiratory symptoms in asthmatic individuals, consistent positive results were observed across

17   studies. Studies consisting of children enrolled in the Childhood Asthma Management Program (CAMP)

18   study found that CO was positively associated with asthma symptoms. Yu et al. (2000) found a 14%

19   increase in asthma symptoms ([95% CI: 5-23] per 0.5 ppm increase in 24-h avg CO concentrations at lag

20   1) in a population of 5-13 year old children (n = 133) with asthma in Seattle, WA. These effects persisted

21   when controlling for previous day's asthma symptoms (12% [95% CI: 5-19] at lag 1). Using the same

22   population of children, Slaughter et al. (2003) found a significant association between short-term

23   exposure to CO at lag 1 and asthma severity both with and without controlling for the previous day's

24   asthma severity, (RR = 1.04 [95% CI: 1.01-1.08]) and (RR = 1.03 [95% CI: 1.00-1.05]), respectively.

25   Schildcrout et al. (2006) examined the association between air pollutants and asthma symptoms in 990

26   children ages 5-12 in 8 North American cities. The authors found a positive association between short-

27   term exposure to CO and asthma symptoms at lag 0 (OR = 1.04 [95% CI: 1.00-1.07] per 0.5 ppm increase

28   in 24-h avg CO), but similar effects were also observed at lag 1, 2, and the 3-day moving sum. The CO

29   effects observed persisted when NO_2, PM_{10}, and SO_2 where included in joint pollutant models.

30   Two additional U.S. studies also found positive associations between CO and asthma symptoms,

31   Rabinovitch et al. (2004) and Delfino et al. (2003). Rabinovitch et al. (2004) found a positive association

32   between 24-h avg CO concentrations for a 3-day moving average (lag 0-2) and asthma exacerbtions (OR

33   = 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

34   with moderate to severe asthma in Denver, CO. Delfino et al. (2003) also observed positive associations

1   between CO and asthma symptoms in a population of Hispanic children with asthma in a Los Angeles,

2   CA, community. However, positive associations were found only when using the previous day's

3   maximum 8-h avg CO concentration as the exposure metric. These results are in contrast to those studies

4   reported above which found positive associations when using 24-h avg CO concentrations as the exposure

5   metric. It should be noted that in comparison to Rabinovitch et al. (2004) and the other studies discussed

6   above, the mean ambient concentrations for 1-h maximum and maximum 8-h avg reported by Delfino et

7   al. (2003) were 7.7 ppm and 5.0 ppm, respectively, both of which are approximately 3.5 times higher than

8   the corresponding 24-h avg concentrations reported in the other studies.

9   In a panel study consisting of 53 adults with asthma or asthma symptoms in Germany, von Klot

10   et al. (2002) observed a marginal association between CO concentration and the prevalence of wheezing

11   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

12   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).

13   However, the authors found CO to be highly correlated with UFP, making it unclear if the effect observed

14   was due to CO alone. Additionally, Park et al. (2005a) in a panel study of individuals 16-75 years old in

15   Incheon, Korea with bronchial asthma did not find an association between CO and nighttime asthma

16   symptoms or cough. Figure 5-11 summarizes the results from studies that provided usable quantitative

17   results and examined the association between short-term exposure to CO and asthma or respiratory

18   symptoms in asthmatic individuals.

19   To further examine the effect of CO on asthma and asthma symptoms some studies also analyzed

20   medication use in asthmatic individuals in response to an increase in air pollution levels. The majority of

21   U.S.-based studies (i.e., Rabinovitch (2004), Slaughter et al. (2003), and Schildcrout et al. (2006))

22   focused on rescue inhaler use in children with ages ranging from 5-13 years old. Rabinovitch et al. (2004)

23   found a weak association (OR = 1.08 [95% CI: 1.00-1.17] per 0.5 ppm increase in 24-h avg CO) between

24   rescue inhaler use in a population of 6-12 year old urban minority children with moderate to severe

25   asthma in the winter in Denver, CO, which is evident by the large confidence intervals surrounding the

26   estimate. Slaughter et al. (2003) in a population of 5-12 year old children with asthma in Seattle, WA

27   found a positive and significant association with rescue inhaler use both with and without taking into

28   consideration the previous day's asthma severity, (RR: 1.04 [95% CI: 1.01-1.08] per 0.5 ppm increase in

29   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.

30   Similar results were observed in a multi-city study conducted by Schildcrout et al. (2006), which analyzed

31   rescue inhaler use in 990 children ages 5-13 with asthma in eight North American cities. Schildcrout et al.

32   (2006) found that short-term exposure to CO was positively associated with rescue inhaler use at lags of

33   0, 2, and a 3-day moving sum, and that the association was fairly robust to an increase in other pollutants

34   (i.e., NO_2, PM_{10}, and SO_2) when included in joint models with CO. However, both Slaughter et al. (2003)

35   and Schildcrout et al. (2006) attributed the associations observed to other combustion byproducts.

36   Additional studies (Park et al., 2005a; Silkoff et al., 2005; von Klot et al., 2002) conducted in Denver,

1   CO; Erfurt, Germany; and Incheon, Korea, respectively, found results that are consistent with those

2   previously reported, but in populations with combined ages ranging from 16-77. Figure 5-11 presents the

3   risk estimates from studies that examined the association between short-term exposure to CO and

4   medication use in asthmatic individuals.

Reference	Location	Population	Age	Lag		
Schildcrout et al. (2006)	8 U.S. cities	Asthmatics (n = 990)	5-12	0-2[a]	Asthma Symptoms	Children
Yu et al. (2000)	Seattle, WA	Mild-to-moderate asthmatics (n = 133)	5-13	1	Asthma Symptoms	
Rabinovitch et al. (2004)	Denver, CO	Asthmatics (n = 147)	6-12	0-2	Asthma Exacerbation	
Delfino et al. (2003)	Los Angeles, CA	Hispanic children with asthma (n = 22)	10-16	1	Symptom Score >2 (1-h max)	
Delfino et al. (2003)	Los Angeles, CA	Hispanic children with asthma (n = 22)	10-16	1	Symptom Score >2 (max 8-h avg)	
(von Klot et al., 2002)	Erfurt, Germany	Asthma/asthma symptoms (n = 53)	37-77	0-5	Wheeze	Adults
Schildcrout et al. (2006)	8 U.S. cities	Asthmatics (n = 990)	5-12	0-2[a]	Inhaler Use	Children
Slaughter et al. (2003)	Seattle, WA	Mild-to-moderate asthmatics n = 133)	5-13	1	Inhaler Use[b]	
Slaughter et al. (2003)	Seattle, WA	Mild-to-moderate asthmatics (n = 133)	5-13	1	Inhaler Use[c]	
Rabinovitch et al. (2004)	Denver, CO	Asthmatics (n = 147)	6-12	0-2	Inhaler Use	
(von Klot et al., 2002)	Erfurt, Germany	Asthma/asthma symptoms (n = 53)	37-77	0-5	Inhaler Use (β2-agonist)	Adults
(von Klot et al., 2002)	Erfurt, Germany	Asthma/asthma symptoms (n = 53)	37-77	0-5	Inhaler Use (Corticosteroid)	

Respiratory Symptoms

Medication Use

0.5   1.0   1.5   2.0   2.5   3.0   4.0

Odds Ratios

[a] Sum of 0-, 1-, and 2-day lags.
[b] Estimate from model that did not control for previous day's asthma severity.
[b] Estimate from model that controlled for previous day's asthma severity.

Figure 5-11.   Asthma symptoms, respiratory symptoms and medication use in asthmatic individuals associated with short-term exposure to CO[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 Non-Asthmatic Individuals

5   In addition to examining the association between short-term exposure to CO and respiratory

6   symptoms (e.g., cough, wheeze, shortness of breath, etc.) in asthmatic populations some studies examined

7   these respiratory effects in individuals classified as non-asthmatics. Rodriguez et al. (2007) and de Hartog

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[1] Effect estimates from Park et al. (2005a) were not included in this figure because the study did not provide the increment at which the effect estimates were calculated.

1   et al. (2003) examined the effect of CO on respiratory symptoms in a panel of 263 children 0-5 years old

2   at high risk for developing asthma in Perth, Australia, and a 3-city panel of individuals $\geq$ 50 years of age

3   with CHD during the winter in Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland,

4   respectively. Rodriguez et al., (2007) found CO concentrations to be positively associated with

5   wheeze/rattle chest and runny/blocked nose at both a 5-day lag and a 0-5-day lag in Perth, Australia. It is

6   unclear which pollutant is driving the effect observed by Rodriguez et al. (2007) because multipollutant

7   models were not examined and additional analyses were not conducted to further characterize the

8   associations observed.

9   In a panel of elderly individuals with CHF in three European locations, de Hartog et al. (2003)

10   observed some marginal associations, specifically between CO concentration and the prevalence of the

11   respiratory symptom shortness of breath, at lag 3 and 0-5-days. Although a marginal association was

12   observed, the authors found that the associations between air pollution exposure and respiratory

13   symptoms were stronger for $PM_{2.5}$ than for gaseous air pollutants.

Summary of Associations between Short-Term Exposure to CO and Pulmonary Function, Respiratory Symptoms, and Medication Use

14   A limited body of evidence is available that examined the effect of short-term exposure to CO on

15   various respiratory health outcomes. Among asthmatics, the studies reviewed generally find positive

16   associations between short-term exposure to CO and respiratory-related health effects (i.e., decrements in

17   lung function/lung function growth, respiratory symptoms, and medication use). It is difficult to

18   determine from this group of studies if CO is independently associated with respiratory outcomes or if

19   CO is an indicator for other traffic-related pollutants. On-road vehicle exhaust emissions are a nearly

20   ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor

21   to CO-related health effects in near-road locations. A lack of copollutant analyses among this group of

22   studies complicates the efforts to disentangle the health effects attributed to CO from the larger traffic-

23   related pollutant mix. Additional uncertainty exists as to a biologically plausible mechanism which could

24   explain the effect of CO on respiratory health.

5.5.1.2. Respiratory Hospital Admissions, ED Visits and Physician Visits

25   The 2000 CO AQCD (U.S. EPA, 2000) evaluated a limited amount of literature that examined the

26   association between short-term exposure to CO and respiratory hospital admissions, ED visits, and

27   physician visits in the U.S. (i.e., Seattle, WA, Reno, NV, and Anchorage, AK) and Europe (i.e., Barcelona,

28   Spain). From these studies, the 2000 CO AQCD concluded that positive associations were observed for

29   short-term exposure to CO with several respiratory outcomes, including asthma and COPD. However, the

1   lack of a biologically plausible mechanism for CO-induced respiratory morbidity at that time brought into
2   question the validity of the results observed.

3   Since the 2000 CO AQCD, the number of studies that examined the association between short-term
4   exposure to CO and respiratory morbidity has increased; however, the total number of studies published is
5   still considerably less than the number that examine the health effects associated with exposure to other
6   criteria air pollutants. This section focuses primarily on those studies conducted in the U.S. and Canada
7   which examined the potential respiratory health effects associated with CO at concentrations at or similar
8   to those found in the U.S. Unlike previous sections, which also evaluated studies conducted outside of the
9   U.S., the expansive U.S.-based respiratory hospital admission and ED visits literature provides adequate
10   evidence to examine the association between short-term exposure to CO and respiratory HA and ED
11   visits. Collectively, the studies conducted outside of the U.S. observed associations that are consistent
12   with those observed in the U.S.-based studies evaluated below (see Annex C).

13   Overall, this section focuses on respiratory-related hospital admissions because the majority of the
14   literature examines hospital admissions as opposed to ED visits or physician visits (Table 5-15 presents
15   the studies evaluated in this section along with the range of CO concentrations measured in each study). It
16   must be noted that when examining the association between short-term exposure to CO and health
17   outcomes that require medical attention, it is important to distinguish between hospital admissions, ED
18   visits, and physician visits for respiratory outcomes (more so than for cardiovascular outcomes). This is
19   because it is likely that a small percentage of respiratory ED visits will be admitted to the hospital and,
20   therefore, may represent potentially less serious, but more common outcomes. To adequately distinguish
21   between the results presented in hospital admission, ED visit, and physician visit studies, each outcome is
22   evaluated in individual sections. In addition, each section presents results separately for respiratory health
23   outcomes which includes all respiratory diagnoses (ICD-9: 460-519) or selected diseases (e.g., asthma,
24   COPD, pneumonia and other respiratory infections) in order to evaluate the potential effect of short-term
25   exposure to CO on each outcome.

Table 5-15.   Range of CO concentrations reported in key respiratory hospital admission and ED visit studies that examine effects associated with short-term exposure to CO.

Author	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Cakmak et al. (2006a)	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)	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;

Author	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Slaughter et al. (2005)	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)	Toronto, ON, Canada	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)	Vancouver, BC, Canada	Hospital Admissions: Respiratory diseases	24-h avg	0.98	50th: 0.82; 75th: 1.16 Maximum: 4.90
Lin et al. (2003)	Toronto, ON, Canada	Hospital Admissions: Asthma	24-h avg	1.18	50th: 1.10; 75th: 1.40 Maximum: 6.10
Lin et al. (2004c)	Vancouver, BC, Canada	Hospital Admissions: Asthma	24-h avg	0.96	50th: 0.80; 75th: 1.12 Maximum: 4.90
Moolgavkar (2003a) (re-analysis of Moolgavkar 2000a)	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)	Vancouver, BC, Canada	Hospital Admissions: COPD	24-h avg	0.71	50th: 0.64 Maximum: 2.48
Karr et al. (2006)	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
Karr et al. (2007)	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)	Boston, MA	Hospital Admissions: Pneumonia	24-h avg	NR	50th: 0.48; 75th: 0.60; 95th: 0.88
Lin et al. (2005)	Toronto, ON, Canada	Hospital Admissions: Respiratory infections	24-h avg	1.16	50th: 1.05; 75th: 1.37 Maximum: 2.45

Author	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Peel et al. (2005)	Atlanta, GA	ED Visits: All respiratory; Asthma; COPD; URI; Pneumonia	1-h max	1.8	90th: 3.4
Tolbert et al. (2007)	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)	New York, NY	ED Visits: Asthma	8-h max	1.31	50th: 1.23; 75th: 1.52; 95th: 2.11
Villeneuve et al. (2006b)	Toronto, ON, Canada	Physicians Visits: Allergic rhinitis	24-h avg	1.1	Maximum: 2.2

Hospital Admissions

Respiratory Disease

1   All but two of the published hospital admission studies that examined the association between
2   short-term exposure to CO and all respiratory diseases from North America were conducted in Canada,
3   and only one study presented results from a combined analysis of multiple cities (Cakmak et al., 2006b).
4   In a study of 10 of the largest Canadian cities, Cakmak et al. (2006b) examined respiratory hospital
5   admissions (ICD-9: 466, 480-486, 490-494, 496) in relation to ambient gaseous pollutant concentrations
6   for the time period 1993-2000. This study reported a 0.37% (95% CI: 0.12-0.50) increase in respiratory
7   hospital admissions for all ages for a 0.5 ppm increase in 24-h avg CO (lag 2.8 days averaged over the 10
8   cities[1]). U.S.-based studies (Los Angeles and Spokane) reported similarly weak or null associations for
9   respiratory disease hospital admissions (Linn et al., 2000; Slaughter et al., 2005). In a study conducted in
10   Toronto, Canada for the time period 1980-1994, Burnett et al. (2001) reported a relatively strong
11   association between 1-h max CO and respiratory disease hospital admissions in children less than two
12   years of age, for the diagnoses of asthma (493), acute bronchitis/bronchiolitis (466), croup (464.4), and
13   pneumonia (480-486). The authors found a 9.7% (95% CI: 4.1-15.5) increase in hospital admissions for a
14   2-day avg (lag 0-1) per 1 ppm increase in 1-h max CO. In the two-pollutant model analysis, the estimates
15   for both CO and O_3 remained elevated. Yang et al. (2003) reported similar results (OR = 1.04
16   [95% CI: 1.01-1.06] at lag 1 per 0.5 ppm increase in 24-h avg CO) for pediatric (<3 years of age)
17   respiratory disease (ICD-9: 460-519) admissions in Vancouver for the time period 1986-1998. Yang et al.
18   (2003) also reported elevated associations with 24-h avg CO and respiratory hospital admissions (ICD-9:
19   codes 460-519) for ages 65 and over in Vancouver, Canada (OR = 1.02 [95% CI: 1.00-1.04]) at lag 1 for a
20   0.5 ppm increase in 24-h avg CO. The authors found that the risk estimate remained elevated when O_3
21   was included in the model.

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[1] To determine the lag for the combined estimate across all 10 cities, Cakmak et al. averaged the strongest associations from lags 0-5 days from each city.

Asthma

1   Some studies that examined the effect of short-term exposure to CO on asthma hospital admissions
2   conducted all age and age-stratified analyses, specifically to examine effects in children. In two of these
3   hospital admission studies conducted in Canada, evidence was observed for increased pediatric (ages
4   6-12) asthma hospital admissions (ICD-9: 493) in boys, but not girls (Lin et al., 2003; 2004c); however, a
5   biological explanation was not provided which could explain this difference. Lin et al. (2003) used a bi-
6   directional case-crossover analysis in Toronto, Canada for the years 1981–1993 reported an OR of 1.05
7   (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
8   being reported when averaging CO concentrations up to 7 days prior to hospitalization. Risk estimates for
9   girls did not provide evidence of an association using the same lag structure that was used in the boys'
10   analysis (OR = 1.00 [95% CI: 0.93-1.06]); lag 1). In a copollutant analysis, the estimates for boys were
11   essentially unchanged when adjusting for all PM indices (Lin et al., 2003). It should be noted that this
12   study used a bi-directional case-crossover analysis, which may be biased (Levy et al., 2001). Studies that
13   examined the various referent selection strategies for the case-crossover study design have concluded that
14   the preferred control selection strategy is the time-stratified framework (Levy et al., 2001). In an
15   additional analysis conducted by Lin et al. (2004c), the authors found less consistent evidence for a
16   greater effect in boys versus girls in Vancouver during the years 1987-1998 using a time-series study
17   design that stratified results by socioeconomic status (SES). In one additional study that examined asthma
18   hospital admissions for all ages and genders combined, Slaughter et al. (2005) observed some evidence of
19   an increase in asthma hospital admissions (ICD-9 493) in Spokane (1995-2000) for CO at lag 2 (RR =
20   1.03 [95% CI: 0.98-1.08]) for a 0.5 ppm increase in 24--h avg, but not for the other two lags examined
21   (lag 1 and lag 3).

Chronic Obstructive Pulmonary Disease

22   A few of the studies examined the effect of short-term exposure to CO on COPD, or obstructive
23   lung disease, and hospital admissions. Moolgavkar (2003a) (a reanalysis of (Moolgavkar, 2000a)
24   examined hospital admissions for COPD plus "allied diseases" (ICD-9 490-496) in two U.S. counties
25   (Cook County, IL and Los Angeles County, CA) for the years 1987-1995 using Poisson generalized linear
26   models (GLMs) or generalized additive models (GAM) with the more stringent convergence criteria.
27   Overall, the results from both models were similar. Using the GAM models the study reported percent
28   increases of 0.53-1.20% for all ages in Los Angeles County, and 0.17-1.41% for ages 65 and older in
29   Cook County, for a 0.5 ppm increase in 24-h avg CO and lags ranging from 0 to 5 days. Yang et al. (2005)
30   reported similar results for COPD hospital admissions (ICD-9 490-492, 494, 496) in Vancouver for ages
31   65 and older for the years 1994-1998 for a moving average of 0-6 day lags (RR = 1.14 [95% CI: 1.03-
32   1.23] per 0.5 ppm increase in 24-h avg CO). However, Slaughter et al. (2005) found no association
33   between short-term exposure to CO and COPD hospital admissions (ICD-9 491, 492, 494, 496) in

1   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

2   similar results being reported for 2- and 3-day lags.

Acute Bronchiolitis in Infants

3   Two studies (Karr et al., 2006; 2007) from the South Coast Air Basin in California examined both

4   short term (lag 0 or 1) and longer term levels of CO in relation to acute bronchiolitis (ICD-9: 466)

5   hospital admissions during the first year of life from 1995-2000. Karr et al. (2006) found no evidence of a

6   short-term association between ambient CO concentrations and hospital admissions for acute bronchiolitis

7   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.

8   (2007), which examined longer term exposures (average in the month prior to hospitalization and lifetime

9   average) in a matched case-control study, also did not provide any evidence of an association with CO.

Pneumonia and Other Respiratory Infections

10   In addition to examining the effect of short-term exposure to CO on health outcomes that can limit

11   the function of the respiratory system, some studies examined the effect of CO on individuals with

12   pneumonia (ICD-9: 480-486) separately or in combination with other respiratory infections. Zanobetti

13   and Schwartz (2006) examined pneumonia hospital admissions (ICD-9 480-487) in Boston, MA, for the

14   years 1995-1999 for ages 65 and older using a time-stratified case-crossover analysis. The authors

15   reported an increase in pneumonia hospital admissions at lag 0 of 5.4% (95% CI: 1.2-10.0) per 0.5 ppm

16   increase in 24-h avg CO. While Zanobetti and Schwartz (2006) did not report multipollutant results, they

17   suggested that CO was most likely acting as a marker for traffic-related pollutants because CO was highly

18   correlated with both BC (r = 0.80) and NO_2 (r = 0.67), and moderately correlated with $PM_{2.5}$ (r = 0.52).

19   Instead of examining the effect of CO on pneumonia hospital admissions separately as was done by

20   Zanobetti and Schwartz (2006), Lin et al. (2005) presented results for the overall effect of CO on

21   respiratory infection hospital admissions (ICD-9: 464, 466, 480-487). In this analysis, Lin et al. (2005)

22   examined the potential increase in respiratory hospital admissions in children less than 15 years of age in

23   Toronto, Canada for 1998-2001 using a bi-directional case-crossover approach. The authors reported

24   elevated estimates for boys (OR = 1.15 [95% CI: 1.02-1.29] per 0.5 ppm increase in 24-h avg CO for a 6-

25   day ma) while the estimate for girls was weaker and with wider confidence intervals (OR = 1.06 [95%CI:

26   0.92-1.21]). Lin et al. (2005) did not provide an explanation as to why the estimates are stronger for boys

27   than for girls. It should be noted that this study used a bi-directional case-crossover analysis, which may

28   be biased (Levy et al., 2001). Studies that have examined the various referent selection strategies for the

29   case-crossover study design have concluded that the preferred control selection strategy is the time-

30   stratified framework (Levy et al., 2001).

Endpoint	Reference	Location	Age	Lag	
All Respiratory	Burnett et al. (2001)	Toronto, CAN	<2	0-1	
	Yang et al. (2003)	Vancouver, CAN	<3	1	
	Linn et al. (2000)	Los Angeles, CA	30+	0	
	Yang et al. (2003)	Vancouver, CAN	65+	1	
	Cakmak et al. (2006b)	10 Canadian Cities	All	2.8	
	Slaughter et al. (2005)	Spokane, WA	All	2	
Asthma	Lin et al. (2003)	Toronto, CAN	6-12	1	Boys
	Lin et al. (2003)	Toronto, CAN	6-12	1	Girls
	Slaughter et al. (2005)	Spokane, WA	All	2	
COPD	Slaughter et al. (2005)	Spokane, WA	15+	2	
	Yang et al. (2003)	Vancouver, CAN	65+	0-6	
Pneumonia	Zanobetti and Schwartz (2006)	Boston, MA	65+	0	
Acute Bronchiolitis	Karr et al. (2006)	SQAB, CA	<1	1	
Respiratory Infection	Lin et al. (2005)	Toronto, CAN	<15	0-5	Boys
	Lin et al. (2005)	Toronto, CAN	<15	0-5	Girls

Figure 5-12. **Summary of associations between 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

1   Peel et al. (2005) conducted a large single-city ED study in Atlanta, GA, which included data from
2 31 hospitals for the time period 1993–2000. In this study, results were reported for various respiratory-

[1] Risk estimates from Moolgavkar (2003a) 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. (2004c) 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).

1   related visits (ICD-9 460-466, 477, 480-486, 491-493, 496, 786.09). In an all ages analysis, the authors

2   found a RR of 1.011 (95% CI: 1.004-1.019) for a 3-day avg (lag 0-2) per 1 ppm increase in 1-h max CO

3   concentration for all respiratory diseases. Tolbert et al. (2007) expanded the time period used in the Peel

4   et al. (2005) study to include ED visits through 2004, and reported similar results for respiratory ED visits

5   (RR: 1.013 [95% CI: 1.007-1.018] per 1 ppm increase in 1-h max CO). The CO risk estimates from the

6   Atlanta, GA, ED visits studies were attenuated when O_3, NO_2, or PM were added to the model (). In

7   addition, Tolbert et al. (2007) reported high correlations between CO and NO_2 (r = 0.70) and EC

8   (r = 0.66); and a moderate correlation with $PM_{2.5}$ (r = 0.51). One additional ED visits study that also

9   examined respiratory disease (Slaughter et al., 2005) presented essentially null results at lag 1 and 2, but

10 found similar results to Peel et al. (2005) and Tolbert et al. (2007) at lag 3 (RR = 1.02 [95% CI: 1.00-1.03]

11 per 0.5 ppm increase in 24-h avg CO).

Asthma

12   The association between short-term exposure to CO and asthma ED visits (ICD-9 493, 786.09) was

13 also examined in Atlanta, GA by Peel et al. (2005). In this study the authors reported results from

14 distributed lag models including lags 0-13 in addition to a moving average of lags 0, 1, and 2 (lag 0-2) for

15 specific respiratory outcomes (e.g., asthma). Effect estimates from the distributed lag models were

16 stronger than those produced from models that used 3-day moving average CO concentrations (RR =

17 1.010 [95% CI: 0.999-1.022] for lags 0-2 compared to RR = 1.076 [95% CI: 1.047-1.105] for an

18 unconstrained distributed lag of 0-13 for a 1 ppm increase in 1-h max CO). These results demonstrated

19 the potential effect of CO exposures up to 13 days prior to an asthma ED visit. Estimates were stronger

20 for pediatric ED visits (ages 2-18 years) (RR = 1.019 [95% CI: 1.004-1.035] per 1 ppm increase in 1-h

21 max CO) for a 3-day avg (lag 0-2) compared to all ages (Peel et al., 2005). Slaughter et al. (2005), which

22 also examined ED visits for Spokane (1995-2001), reported an increase in asthma ED visits for all ages

23 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

24 other two lags examined (lags 1 and 2). The results from Ito et al. (2007) also provide evidence of

25 increased ED visits for asthma (ICD-9 493) for all ages in New York City for 1999-2002, but quantitative

26 results were not provided. In addition, Ito et al. (2007) stated that increased CO effect estimates were

27 attenuated when NO_2 was included in the model, but effect estimates remained elevated in two-pollutant

28 models with either $PM_{2.5}$ or O_3.

Chronic Obstructive Pulmonary Disease

29   In the examination of the effect of short-term exposure to CO on COPD ED visits (ICD-9 491, 492,

30 496), Peel et al. (2005) reported elevated estimates for Atlanta, GA for 1993-2000 (RR = 1.03 [95%CI:

31 1.00-1.05] per 1 ppm increase in 1-h max CO for a moving average of lag 0-2) with similar results for the

32 distributed lag model (RR = 1.03 [95% CI: 0.98-1.09). However, results from Slaughter et al. (2005) from

1 Spokane were consistent with a null or slightly protective association at lag 1 (RR = 0.96

2 [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

3 Similar to the hospital admission analysis conducted by Zanobetti and Schwartz (2006) discussed

4 above, Peel et al. (2005) examined the effect of CO on pneumonia separately (ICD-9: 480-486), but also

5 included an analysis of upper respiratory infection (ICD-9: 460-466, 477) ED visits for all ages in Atlanta,

6 GA during the years 1993-2000. The authors reported a weak estimate for pneumonia for the three-day

7 moving average (lag 0-2) (RR = 1.01 [95% CI: 0.996-1.021] per 1 ppm increase in 1-h max CO).

8 However, when using an unconstrained distributed lag (days 0-13), Peel et al. (2005) observed evidence

9 of an association (RR = 1.045 [95% CI: 1.01-1.08]). An examination of URI ED visits, the largest of the

10 respiratory ED groups, found slightly increased risk estimates for both the three-day moving average

11 (lag 0-2) (RR = 1.01 [95% CI: 1.00-1.02]) and the unconstrained distributed lag for days 0-13 (RR = 1.07

12 [95% CI: 1.05-1.09]) per 1 ppm increase in 1-h max CO. In copollutant models, CO risk estimates were

13 largely attenuated when PM_{10}, O_3, or NO_2 were included in the model. Upon conducting an age-stratifed

14 analysis, Peel et al. (2005) also found that infant (less than one year of age) and pediatric (ages 2-18) URI

15 ED visit CO risk estimates were substantially stronger than all age risk estimates.

Endpoint	Reference	Location	Age	Lag	
All Respiratory	Slaughter et al. (2005)	Spokane, WA	All	3	
	Peel et al. (2005)	Atlanta, GA	All	0-2	
	Tolbert et al. (2007)	Atlanta, GA	All	0-2	
Asthma	Peel et al. (2005)	Atlanta, GA	2-18	0-2	
	Peel et al. (2005)	Atlanta, GA	All	0-2	
	Peel et al. (2005)	Atlanta, GA	All	0-13*	
	Slaughter et al. (2005)	Spokane, WA	All	3	
COPD	Slaughter et al. (2005)	Spokane, WA	15+	1	
	Peel et al. (2005)	Atlanta, GA	All	0-2	
	Peel et al. (2005)	Atlanta, GA	All	0-13*	
Pneumonia	Peel et al. (2005)	Atlanta, GA	All	0-2	
	Peel et al. (2005)	Atlanta, GA	All	0-13*	
Respiratory Infection	Peel et al. (2005)	Atlanta, GA	All	0-2	
	Peel et al. (2005)	Atlanta, GA	All	0-13*	

* Unconstrained distributed lag

Effect Estimates (x-axis: 0.90, 0.95, 1.00, 1.05, 1.10, 1.15)

Figure 5-13. Summary of associations between 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

1   Although hospital admissions and ED visits are the two most well studied measures of morbidity, a
2   few studies also examined the effect of CO on unscheduled physician visits. In a time-series study,
3   Villeneuve et al. (2006b) examined the effect of CO on physician visits for allergic rhinitis in individuals
4   65 and older in Toronto, Canada. Although quantitative results were only presented in figures, upon
5   observation it was evident that estimates were consistent with a null association for lags 0-6 (Villeneuve
6   et al., 2006b). In an additional study, Sinclair et al. (2004) reported results for urgent care visits for asthma
7   and respiratory infections in a health maintenance organization in Atlanta, GA; however, the study only
8   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

1   Relatively few studies evaluated the association between short-term exposure to ambient CO and
2   hospital admissions and ED visits for various respiratory outcomes compared to other criteria air
3   pollutants (e.g., O_3 and PM). Although evidence for consistent positive associations (See Figures 5-12 and
4   5-13) has been found across these studies, various issues surrounding the association between short-term
5   exposure to CO and respiratory-related health effects have not been addressed due to: the lack of studies
6   that examined potential confounders of the CO-respiratory hospital admission and ED visits relationship;
7   and uncertainty as to a biologically plausible mechanism which could explain the association between CO
8   exposure and respiratory-related health effects. Some of the studies evaluated suggest that CO acts as an
9   indicator of combustion (e.g., traffic), which is supported by the moderate to high correlation between CO
10   and other traffic-related pollutants such as NO_2, $PM_{2.5}$, EC, or BC and in addition complicates the results
11   presented. Only two studies examined potential confounding of CO risk estimates by other pollutants
12   through copollutant models, and found that CO risk estimates were robust or attenuated but remained
13   positive in two-pollutant models with O_3, NO_2, or PM indices.

5.5.2. Epidemiologic Studies with Long-Term Exposure

14   The 2000 CO AQCD did not evaluate any studies that examined the effect of long-term exposure to
15   CO on respiratory health. The following section discusses those studies that analyze the effect of long-
16   term exposure to CO on pulmonary function, asthma/asthma symptoms, and allergic rhinitis.

5.5.2.1. Pulmonary Function

17   Mortimer et al. (2008) examined the effect of prenatal and lifetime exposures to air pollutants on
18   pulmonary function in 232 asthmatic children that resided in the San Joaquin Valley of California. The
19   strong temporal correlation between pollutants and pollutant metrics for different time periods in the
20   study area contributed to the inability to draw conclusions about the effect of individual pollutant metrics
21   on pulmonary function (Mortimer et al., 2008). In an attempt to remedy this problem the authors used a
22   newly developed Deletion/Substitution/Addition (DSA) algorithm "to identify which pollutant metrics
23   were most predictive of pulmonary function" (Mortimer et al., 2008). This methodology uses an
24   exploratory process to identify the best predictive model for each outcome of interest. Using this
25   approach, Mortimer et al. (2008) found that exposure to CO early in life (ages 0-3) was negatively
26   associated with FEV_1/FVC and FEF_{25-75}/FVC resulting in an effect size of -2.5% and -4.8%, respectively,

1   per IQR increase in CO.[1] Additional negative associations were observed between exposure to CO during

2   the first 6 years of life and FEF_{25} (-6.7%), and prenatal, not trimester-specific exposure, and FEF_{25-75} (%

3   reduction not reported). Overall, Mortimer et al. (2008) found that the effects were limited to subgroups,

4   including African Americans, individuals diagnosed with asthma before the age of 2 years, and

5   individuals exposed to maternal smoking during pregnancy. It must be noted that research still needs to be

6   conducted to validate the aforementioned results obtained using the DSA algorithm and the subsequent

7   calculation of effect estimates using GEE because the current model could underestimate the uncertainty

8   surrounding the associations reported (Mortimer et al., 2008). Although the authors did find associations

9   between long-term exposure to CO and decrements in pulmonary function, they also observed high

10   correlations between CO and NO_2, which together are markers for pollutants generated by urban

11   combustion sources (e.g., mobile sources) (Mortimer et al., 2008).

5.5.2.2. Asthma and Asthma Symptoms

12   All of the studies that examined the association between long-term exposure to CO and asthma

13   and/or asthma symptoms presented consistent, positive results, which is similar to what was observed

14   when evaluating the effects attributed to short-term exposure to CO. Two U.S.-based studies, Goss et al.

15   (2004) and Meng et al. (2007), were evaluated which examined the effect of long-term exposure to CO

16   on: (1) pulmonary exacerbations in a cohort of individuals with cystic fibrosis >6 years of age, and (2)

17   poorly controlled asthma in a population of asthmatics $\geq$ 18 years old that resided close to cross-street

18   intersections in Los Angeles County and San Diego County, respectively. Of these two studies only Goss

19   et al. (2004) observed a positive association between a respiratory outcome (i.e., pulmonary

20   exacerbations) and long-term exposure to CO. However, it is unclear if the effects observed are due to CO

21   alone because the authors did not conduct co-pollutant analyses.

22   When evaluating studies conducted in other countries, Hirsch et al. (1999), in a study conducted in

23   Germany, and Guo et al. (1999), Wang et al. (1999), and Hwang et al. (2005), in studies conducted in

24   Taiwan, all found positive associations between long-term exposure to CO and asthma or asthma

25   symptoms in populations ranging from 6–16 years old. In these studies, the authors addressed the

26   observed associations differently. Guo et al. (1999) and Hwang et al. (2005) both concluded that it is

27   unlikely CO directly affects the respiratory system; Hirsch et al. (1999) attributed the increase in the

28   prevalence of cough and bronchitis to exposure to traffic-related air pollutants (i.e., NO_2, CO, and

29   benzene); and Wang et al. (1999) did not interpret the association between long-term exposure to CO and

30   adolescent asthma. Only Hwang et al. (2005) conducted a co-pollutant analysis and found that the asthma

31   effects observed were robust to the inclusion of PM_{10}, SO_2 and O_3 in the model. This is of note because

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[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.

1   inclusion of the traffic-related pollutants NO_X or NO_2 in some of the aforementioned studies complicated

2   the overall results because NO_X and NO_2 are highly correlated with CO, which makes it difficult to

3   separate the effects attributed to each pollutant.

5.5.2.3. Allergic Rhinitis

4   Hwang et al. (2006) and Lee et al. (2003c) both examined the effect of long-term exposure to air

5   pollutants on the prevalence of allergic rhinitis in a population of schoolchildren in Taiwan. Both studies

6   found an association between allergic rhinitis prevalence and CO, but they also observed an association

7   with NO_X. As a result, although Hwang et al. (2006) and Lee et al. (2003c) observed an increase in the

8   prevalence of allergic rhinitis in response to an increase in long-term CO levels, they concluded that the

9   combination of an association being observed for both CO and NO_X can be attributed to the complex

10   mixture of traffic-related pollutants and not necessarily CO alone.

5.5.2.4. Summary of Associations between Long-Term Exposure to CO and Respiratory Morbidity

11   To date, a limited number of studies have examined the potential association between long-term

12   exposure to CO and respiratory morbidity. Although studies have reported positive associations for

13   various respiratory outcomes, the limited evidence available, the new analytical methods employed, and

14   the lack of studies that examined potential confounders of the CO-respiratory morbidity relationship,

15   especially due to the high correlation between CO and other traffic-related pollutants, brings into question

16   the validity of the associations observed.

5.5.3. Controlled Human Exposure Studies

17   Human clinical studies provide very little and inconsistent evidence of changes in pulmonary

18   function following exposure to CO. In one older study, Chevalier et al. (1966) observed a significant

19   decrease in total lung capacity following a short term exposure to 5,000 ppm resulting in a COHb level of

20   4%. However, a similar study conducted at a higher CO concentration resulting in COHb levels of

21   17-19% found no CO-induced changes in lung volume or mechanics (Fisher et al., 1969). The 2000 CO

22   AQCD reported no evidence of CO-induced changes in exercise ventilation at COHb levels <15% during

23   submaximal exercise (Koike et al., 1991). In two recent human clinical studies, exposure to CO (COHb ≈

24   10%) was not found to significantly affect resting pulmonary ventilation compared with exposure to clean

25   air under either hypoxic or hyperoxic exposure conditions (Ren et al., 2001; Vesely et al., 2004)`. The

26   results of these studies demonstrate that the hypoxia- and CO_2-induced increases in pulmonary ventilation

1   are not affected by CO. One recent study evaluated the potential anti-inflammatory effects of controlled

2   exposures to CO in the airways of 19 individuals with COPD (Bathoorn et al., 2007). Subjects were

3   exposed to both CO at concentrations of 100-125 ppm as well as room air for 2 h on each of four

4   consecutive days. The authors reported a small decrease in sputum eosinophils, as well as a slight increase

5   in the provocative concentration of methacholine required to cause a 20% reduction in FEV_1 following

6   exposure to CO. Although this study appears to demonstrate some evidence of an anti-inflammatory

7   effect of CO among subjects with COPD, it must be noted that two of these patients experienced

8   exacerbations of COPD during or following CO exposure. A similar study found no evidence of systemic

9   anti-inflammatory effects following exposure to higher CO concentrations (500 ppm for 1 h) in a group of

10 healthy adults (Mayr et al., 2005).

5.5.4. Toxicological Studies

11 As discussed in Section 5.2.3., the work of Thom, Ischiropoulos and colleagues (Ischiropoulos et

12 al., 1996; Thom and Ischiropoulos, 1997; Thom et al., 1997; Thom et al., 1999a; Thom et al., 1999b)

13 focused on CO-mediated displacement of $NO^\bullet$ from heme-binding sites. Although the concentrations of

14 CO used in many of their studies were far higher than ambient levels, some of this research involved

15 more environmentally-relevant CO levels. In one study, 1-h exposure of rats to 50 ppm CO resulted in

16 increased lung capillary leakage 18 h later (Thom et al., 1999a). Increased $NO^\bullet$ was observed in the lungs

17 by electron paramagnetic resonance during 1-h exposure to 100 ppm CO and was accompanied by

18 increases in H_2O_2 and nitrotyrosine. All of these effects were blocked by inhibition of NOS. These results,

19 which were partially discussed in the 2000 CO AQCD, demonstrate the potential for exogenous CO to

20 interact with $NO^\bullet$-mediated pathways and to lead to pathophysiological effects in the lung.

21 Recent work by Ghio et al. (2008) showed a disruption of cellular iron homeostasis following

22 exposure to a low level of CO (50 ppm x 24 h) in rats. In lungs of inhalation-exposed rats, non-heme iron

23 was significantly reduced, while lavagable iron was increased dramatically, suggesting an active removal

24 of cellular iron. Lavagable ferritin was also increased following the CO exposure. Concurrently, liver iron

25 levels increased, implying that the anatomical distribution of iron stores may significantly shift

26 during/after CO exposures. These investigators were able to replicate the effect of loss of cellular iron in

27 an in vitro model of cultured BEAS-2B cells and reported statistically significant effects at 10 ppm CO

28 and an apparent maximal effect at 50 ppm CO (concentrations up to 500 ppm did not significantly

29 enhance the iron loss beyond 50 ppm). Similar responses were observed for cellular ferritin. Both

30 enhancement of iron removal and diminished iron uptake were noted in CO-exposed cells. Furthermore,

31 decreased oxidative stress, mediator release and proliferation were noted in respiratory cells. These effects

32 were reversible with a recovery period in fresh air. Interestingly, the in vivo exposure to CO induced mild,

1 but significant neutrophilia in the lungs compared to air-exposed rats. This finding is contrary to the

2 concept that CO acts as an anti-inflammatory agent; however, with alterations in iron handling several

3 potential pathways could be initiated to recruit inflammatory cells into airways. The authors pointed out

4 that while CO derived from HO activity may have an important role in iron regulation, the non-specific

5 application of exogenous CO will have little capacity to discriminate between excessive and/or

6 inappropriate iron which catalyzes oxidative stress and iron which may be required for normal

7 homeostasis.

8   A chronic inhalation study by Sorhaug et al. (2006) demonstrated no alterations in lung

9 morphology in Wistar rats exposed to 200 ppm CO for 72 weeks. COHb levels were reported to be 14.7%

10 and morphological changes were noted in the heart as described in Section 5.2.3.

11   A recent study by Carraway et al. (2002) involved continuous exposure of rats to HH (380 torr)

12 with or without co-exposure to CO (50 ppm) for up to 21 days. The focus of this study was on remodeling

13 of the pulmonary vasculature. While the addition of CO to HH did not alter the thickness or diameter of

14 vessels in the lung, there was a significant increase in the number of small (<50 μm) diameter vessels

15 compared to control, HH only, and CO-only exposures. Despite the greater number of vessels, the overall

16 pulmonary vascular resistance was increased in the combined CO + HH exposure, which the authors

17 attribute to enhancement of muscular arterioles and β-actin.

18   In summary, one older study (Thom et al., 1999a) and two new studies (Carraway et al., 2002; Ghio

19 et al., 2008) demonstrated effects of 50-100 ppm CO on the lung. Responses included an increase in

20 alveolar capillary permeability, disrupted iron homeostasis, mild pulmonary inflammation and an

21 exacerbation of pulmonary vascular remodeling elicited by HH. These results should be considered in

22 view of the potential for inhaled CO to interact directly with lung epithelial cells and resident

23 macrophages. However, a chronic study involving 200 ppm CO demonstrated no changes in pulmonary

24 morphology (Sorhaug et al., 2006).

5.5.5. Summary of Respiratory Health Effects

5.5.5.1. Short-Term Exposure to CO

25   New epidemiologic studies, supported by the body of literature summarized in the 2000 CO

26 AQCD, provide evidence of positive associations between short-term exposure to CO and respiratory-

27 related outcomes including pulmonary function, respiratory symptoms, medication use, hospital

28 admissions, and ED visits. However, the interpretation of the results from epidemiologic studies is

29 difficult due to the lack of extensive copollutant analyses along with the moderate to high correlation

30 between CO and other combustion/traffic generated pollutants. To date the majority of the literature has

31 not extensively examined the association between CO and respiratory morbidity due to studies focusing

1   primarily on effects associated with exposure to other criteria pollutants, namely PM and O_3. This has
2   contributed to the inability to disentangle the effects attributed to CO from the larger complex air
3   pollution mix (particularly motor vehicle emissions). In addition, uncertainty as to a biological
4   mechanism to explain the respiratory-related effects observed in the epidemiologic literature further
5   complicates the interpretation of these results, especially considering the low ambient CO concentrations
6   reported (24-h avg: 0.35-2.1 ppm). However, animal toxicological studies do provide some evidence that
7   short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter
8   pulmonary vascular remodeling. Human clinical studies have not extensively examined the effect of
9   short-term exposure on respiratory morbidity, specifically pulmonary function. The limited number of
10 human clinical studies that have been conducted prior to and since the 2000 CO AQCD provide very little
11 evidence of any adverse effect of CO on the respiratory system at COHb levels <10%. Although human
12 clinical studies have not provided evidence to support CO-related respiratory health effects, the
13 epidemiologic studies that examined the effects of short-term exposure to CO and lung-related outcomes
14 show positive associations and animal toxicological studies demonstrate the potential for an underlying
15 biological mechanism, which together provide **evidence that is suggestive of a causal relationship**
16 **between short-term exposure to relevant CO concentrations and respiratory morbidity.**

5.5.5.2. Long-Term Exposure to CO

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

5.6. Mortality

5.6.1. Epidemiologic Studies with Short-Term Exposure to CO

1   The relationship between short-term exposure to CO and mortality has not been extensively
2   examined over the years due to the majority of epidemiologic studies focusing on mortality effects
3   associated with exposure to PM and O_3. As a result, a clear understanding of the association between
4   short-term exposure to CO and mortality has yet to be developed. This section summarizes the main
5   findings of the 2000 CO AQCD, and evaluates the newly available information on the relationship
6   between short-term exposure to CO and daily mortality in an effort to disentangle the CO-mortality effect
7   from those effects attributed to other criteria air pollutants.

5.6.1.1. Summary of Findings from 2000 CO AQCD

8   The 2000 CO AQCD examined the association between short-term exposure to CO and mortality
9   through the analysis of twelve single-city time-series studies, and one multi-city study, which included 11
10 Canadian cities. While the results presented by these studies did provide suggestive evidence that an
11 association exists between CO and mortality the AQCD concluded that inadequate evidence existed to
12 infer a causal association between mortality and short-term exposure to ambient concentrations of CO.
13 The reasons for this conclusion, which are shared with those studies that examined the effect of short-
14 term exposure to CO on morbidity, were due to: internal inconsistencies and lack of coherence of the
15 reported results within and across studies; the representativeness of the average ambient CO levels of
16 spatially heterogeneous ambient CO values derived from fixed monitoring sites or of personal exposures
17 that often include nonambient CO; and the lack of biological plausibility for any harmful effects
18 occurring with the very small changes in COHb levels (from near 0 up to 1.0%) over typical baseline
19 levels (about 0.5%) that would be expected with the low average ambient CO levels (<5.0 ppm, 1-h daily
20 max) reported in the epidemiologic studies (U.S. EPA, 2000). Additionally, some epidemiologic studies
21 have also suggested that CO is acting as an indicator for other combustion-related pollutants, which has
22 led to investigators questioning the CO-mortality relationship even when associations have been
23 observed.
24   To date the aforementioned issues have not been addressed primarily due to the majority of the
25 recent time-series mortality studies focusing on the effects of only PM and O_3. As such, CO has usually
26 been considered one of the potential confounding copollutants in air pollution epidemiologic studies. As a
27 result, the available CO information from these PM and O_3 studies most frequently consists of risk
28 estimates from single- and multipollutant models. Given the limitation that most of these studies were not

1   conducted to examine CO, the goal of this review is to evaluate the CO-mortality association, and

2   specifically the: magnitude of associations; evidence of confounding; and evidence of effect modification.

5.6.1.2. Multi-City Studies

3   The following sections evaluate the recent literature that examined the association between short-

4   term exposure to CO and mortality, and in addition discuss newly available information with regard to the

5   issues specific to CO mentioned above. This evaluation focuses primarily on multi-city studies because

6   they provide: a more representative sample of potential CO-related mortality effects; and especially useful

7   information by analyzing data from multiple cities using a consistent method, and thus avoiding potential

8   publication bias.[1] Table 5-16 lists the multi-city studies evaluated along with the mean CO concentrations

9   reported in each study.

Table 5-16.   Range of CO concentrations reported in multi-city studies that examine mortality effects associated with short-term exposure to CO.

Author	Location	Years	Averaging Time	Mean Concentration (ppm)	Range of Mean Concentrations Across Cities (ppm)
Dominici et al. (2003b; 2005a) (reanalysis of Samet et al., 2000b)	82 U.S. cities[1] (NMMAPS)	1987-1994	24-h avg	1.02	Baton Rouge = 0.43 Spokane = 2.19
Burnett et al. (2004)	12 Canadian cities	1981-1999	24-h avg	1.02	Winnipeg = 0.58 Toronto = 1.31
Samoli et al. (2007)[2]	19 European cities (APHEA2)	1990-1997[3]	8-h max	2.12	Basel = 0.52 Athens = 5.3

[1] The study actually consisted of 90 U.S. cities, but only 82 had CO data.
[2] 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.
[3] 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

10   The time-series analysis of the largest 90 U.S. cities (82 cities for CO) in the National Morbidity,

11   Mortality, and Air Pollution Study (NMMAPS) Dominici et al. (2003b; 2005a) (reanalysis of Samet et al.,

12   2000b) is by far the largest multi-city study conducted to date to investigate the mortality effects of air

13   pollution, but the study primarily focused on PM_{10}. The range in 24-h avg CO concentrations in the

14   largest 20 cities (by population size) was 0.66 ppm (Detroit, MI) to 2.04 ppm (New York City). The

15   analysis in the original report used GAM with default convergence criteria. In response to the bias

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[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.

1   observed in the estimates generated using GAM models with default convergence criteria (Dominici et

2   al., 2002), Dominici et al. (2003b; 2005a) (reanalysis of Samet et al., 2000b) used the data using GAM

3   with stringent convergence criteria as well as GLM.

4   Focusing on the results obtained using GLM, PM_{10} and O_3 (in summer) appeared to be more

5   strongly associated with mortality than the other gaseous pollutants. The authors stated that the results did

6   not indicate associations of CO, SO_2, or NO_2, with total (non-accidental) mortality. However, as with

7   PM_{10}, the gaseous pollutants CO, SO_2, and NO_2 each showed the strongest association at a 1-day lag (for

8   O_3, a 0-day lag). Figure 5-14 presents the total mortality risk estimates for CO from Dominici et al.

9   (2003b). The authors found a mortality risk estimate of 0.23% (95% PI: 0.09, 0.36) per 0.5 ppm increase

10   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

11   model did not reduce CO risk estimates. However, the confidence bands were wider in the multipollutant

12   models, but this could be attributed to: (1) PM_{10} data in many of the cities being collected every 6th day,

13   as opposed to daily data for gaseous pollutants; and (2) O_3 being collected in some cities only during

14   warm months. The addition of NO_2 (along with PM_{10}) to the model resulted in a reduced CO risk

15   estimate. Some caution is required when interpreting this apparent reduction because a smaller number of

16   cities (57 cities[1]) were available for the CO multipollutant analysis with PM_{10} and NO_2 compared to the

17   single-pollutant CO analysis (82 cities). However, most of the cities that did not have NO_2 data (26 out of

18   32), and subsequently were not included in the multipollutant analysis, were some of the least populated

19   cities. Thus, the difference in the number of cities in the multi- and single-pollutant analyses is unlikely to

20   be the underlying cause for the reduction in the CO risk estimate in the CO multipollutant analysis with

21   PM_{10} and NO_2. In comparison to the PM_{10} risk estimates, which were not reduced in multipollutant

22   models, the CO risk estimates from multipollutant models indicate less consistent associations with

23   mortality.

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[1] One city was excluded from the multipollutant analysis because it contained NO_2 data, but did not contain CO data.
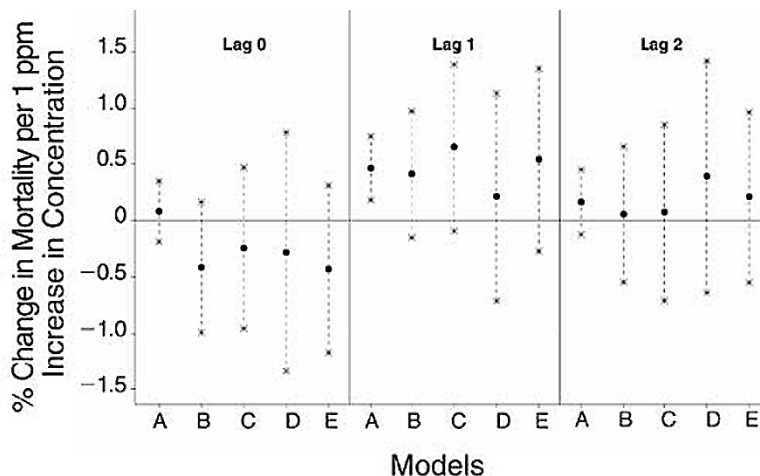
Figure 5-14. **Posterior means and 95% posterior intervals of national average estimates for CO effects on total (non-accidental) mortality at lags 0, 1, and 2 within sets of the 90 U.S. cities with available pollutant data. Models A = CO alone; B = CO + PM_{10}; C = CO + PM_{10} + O_3; D = CO + PM_{10} + NO_2; E = CO + PM_{10} + SO_2.**

Canadian Multi-City Studies

1   Since the 2000 CO AQCD two Canadian multi-city studies have been published that examined the
2   association between mortality and short-term exposure to air pollutants: (1) an analysis of PM_{10}, $PM_{2.5}$,
3    $PM_{10-2.5}$, and gaseous pollutants in 8 cities from 1986 to 1996 (Burnett et al., 2000); and (2) an analysis of
4   PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 12 cities from 1981 to 1999 (Burnett et al., 2004). The
5   2000 study utilized GAM with default convergence criteria, and upon reanalysis only examined PM
6   indices (Burnett and Goldberg, 2003).
7   Burnett et al. (2004) is the most extensive Canadian multi-city study conducted to date, both in
8   terms of the length of the study and the number of cities covered. Although the study focused on NO_2
9   because it was the best predictor of short-term mortality fluctuations among the pollutants examined
10   (NO_2, O_3, SO_2, CO, $PM_{2.5}$, and $PM_{10-2.5}$), it did present single- and copollutant results for all pollutants
11   included in the analysis. The mean CO concentrations reported by Burnett et al. (2004) are similar to
12   those reported in NMMAPS (see Table 5-14).
13   Burnett et al. (2004) examined the effect of short-term exposure to CO on total (non-accidental)
14   mortality. The authors found the strongest mortality association at lag 1-day for CO, SO_2, $PM_{2.5}$, $PM_{10-2.5}$,
15   PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), and CoH, whereas for NO_2, it was the 3-day moving
16   average (i.e., average of 0-, 1-, and 2-day lags), and for O_3, it was the 2-day moving average. In this study,
17   Burnett et al. (2004) used 24-h avg pollutant concentrations because these values showed stronger
18   associations than the daily 1-h max values for all of the gaseous pollutants and CoH, but not for O_3. In a
19   single-pollutant model the CO risk estimate for total mortality was 0.33% (95% CI: 0.12-0.54) per

1   0.5 ppm increase in 24-h avg CO with a 1-day lag. After adjusting for NO_2, the CO risk estimate was

2   reduced to 0.04% (95% CI: -0.19 to 0.26), while the NO_2 risk estimate was only slightly affected

3   (increased from 2.25% to 2.35%) when including CO in the model. In this analysis, a copollutant model

4   including both CO and PM was not presented. The similarity between the results presented in this

5   Canadian multi-city and NMMAPS is that, in both analyses, CO risk estimates appeared to be sensitive to

6   the addition of NO_2 in the regression model. However, interpretation of these results requires some

7   caution because: (1) NO_2 tends to have a more spatially uniform distribution within a city compared to

8   CO; (2) CO and NO_2 share common sources (e.g., traffic); and (3) CO and NO_2 are often moderately to

9   highly correlated.

Air Pollution and Health: A European Approach

10   Most of the Air Pollution and Health: A European Approach (APHEA) analyses have focused on

11   the mortality effects of PM (PM_{10} and BS), SO_2, NO_2, and O_3, but not CO. In addition, some of the

12   analyses have not even considered CO as a potential confounder, such as the extended analysis

13   (APHEA2) of PM (Katsouyanni et al., 2001), and NO_2. One study, Gryparis et al. (Gryparis et al., 2004)

14   did consider CO as a potential confounder in an analysis of O_3, and found that the addition of CO

15   increased O_3 mortality risk estimates both in the summer and winter although the number of cities

16   included in the copollutant model were reduced from 21 to 19. However, the study did not present CO

17   risk estimates. Unlike other APHEA studies (or the NMMAPS and Canadian multi-city studies), the

18   Samoli et al. (2007) analysis focused specifically on CO.

19   Samoli et al. (2007) investigated the effect of short-term exposure to CO on total (non-accidental)

20   and cardiovascular mortality in 19 European cities participating in the APHEA2 project by using a two-

21   stage analysis to examine city-specific effects and potential sources of heterogeneity in CO-mortality risk

22   estimates. The mean levels of the max 8-h avg CO concentration in this study ranged from 0.52 ppm

23   (Basel, Switzerland, and the Netherlands) to 5.3 ppm (Athens, Greece). The max 8-h avg CO

24   concentration for the APHEA2 study of 2.12 ppm is higher than the estimated max 8-h avg CO

25   concentrations reported in U.S. (Dominici et al., 2003b, 2005b) and Canadian (Burnett et al., 2004) cities

26   of 1.53 ppm.[1] In APHEA cities, the correlation between CO and BS (r = 0.67-0.82) was higher than the

27   correlation between CO and PM_{10} (r = 0.16-0.70) or the correlation between CO and 1-h max NO_2

28   (r = 0.03-0.68).

29   To examine the CO-mortality relationship, Samoli et al. (2007) conducted a time-series analysis of

30   individual cities following the revised APHEA2 protocol.[2] The primary results presented by the authors

31   are from a sensitivity analysis that used two alternative methods to select the extent of adjustment for

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[1] The max 8-h avg concentration for the Dominici et al. (2003b) and Burnett et al. (2004) 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.

1 temporal confounding. These methods consisted of: (1) confining the extent of smoothing to 8 degrees of

2 freedom per year (df/yr); and (2) selecting the appropriate extent of smoothing through minimization of

3 the absolute value of the sum of partial auto-correlation functions (PACF) of the residuals, which resulted

4 in the analysis using on average 5 df/yr for total mortality and 4 df/yr for cardiovascular mortality. The

5 authors also conducted copollutant analyses using PM_{10}, BS, SO_2, NO_2, or O_3 (1 h). In the second stage

6 model Samoli et al. (2007) examined heterogeneity in CO risk estimates between cities by regressing risk

7 estimates from individual cities on potential effect modifiers including: a) the air pollution level and mix

8 in each city (i.e., mean levels of pollutants, ratio PM_{10}/NO_2); b) the exposure (number of CO monitors,

9 correlation between monitors' measurements); c) variables describing the health status of the population

10 (e.g., crude mortality rate); d) the geographic area (northern, western, and central-eastern European

11 cities); and e) the climatic conditions (mean temperature and relative humidity levels).

12   Samoli et al. (2007) found that CO was associated with total and cardiovascular mortality. The

13 primary results represent the combined random effects estimate for a 0.75 ppm increase in max 8-h avg

14 CO concentrations for the average of 0- and 1-day lag for total mortality (1.03% [95% CI: 0.55-1.53]) and

15 for cardiovascular mortality (1.08% [95% CI: 0.25-1.90]). These results were obtained using PACF to

16 choose the extent of adjustment for temporal trends. Although the results obtained using PACF are

17 insightful, the use of 8 df/yr would have been more consistent with the NMMAPS model (7 df/yr), and

18 would have allowed for a more accurate comparison of the results between APHEA2 and NMMAPS. The

19 corresponding risk estimates obtained using the 8 df/yr model are: 0.57% (95% CI: 0.23-0.91) for total

20 mortality and 0.70% (95% CI: 0.31-1.09) for cardiovascular mortality. In the sensitivity analysis, Samoli

21 et al. (2007) used 8 or 12 df/yr to adjust for temporal confounding. Both approaches led to similar risk

22 estimates, but using PACF to choose the extent of smoothing generally resulted in larger CO risk

23 estimates (by ~50 to 80%).

24   During the examination of results obtained from the copollutant models, the authors noted that

25 there was indication of confounding of CO risk estimates by BS and NO_2, but not PM_{10}. These results are

26 consistent with CO, BS, and NO_2 being part of the traffic pollution mixture and PM_{10} likely including

27 secondary aerosols that do not correlate well with traffic-derived pollution. The risk estimates from the

28 model using 8 df/yr that included NO_2 were: 0.26% (-0.09 to 0.61) for total mortality and 0.37% (-0.05 to

29 0.80) for cardiovascular mortality. Thus, the inclusion of NO_2 in the model nearly halved the CO risk

30 estimates (whereas the NO_2 risk estimate was not sensitive to the inclusion of CO in the model). A similar

31 magnitude of reduction in the CO risk estimates was also observed when including BS in the model.

32 Overall, the sensitivity of CO risk estimates to the inclusion of NO_2 in the model is consistent with the

33 results presented in NMMAPS and the Canadian multi-city studies.

34   In the second stage model, Samoli et al. (2007) found that geographic region was the most

35 significant effect modifier, while the other effect modifiers (mentioned above) did not result in strong

36 associations. Effects were primarily found in western and southern European cities, and were larger in

1   cities where the standardized mortality rate was lower. Earlier APHEA studies also reported a regional
2   pattern of air pollution associations for BS and SO_2, and found that western cities showed stronger
3   associations than eastern cities. However, the heterogeneity in CO risk estimates by geographic region
4   does not provide specific information to evaluate the CO-mortality association.

5   An ancillary analysis conducted by Samoli et al. (2007) examined the possible presence of a CO
6   threshold. The authors compared city-specific models to the threshold model, which consisted of
7   thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007) then computed the deviance between
8   the two models and summed the deviances for a given threshold over all cities. While the minimum
9   deviance suggested a potential threshold of 0.43 ppm (the lowest threshold examined), the comparison
10   with the linear no-threshold model indicated weak evidence (p-value >0.9) for a threshold. However,
11   determining the presence of a threshold at the very low range of CO concentrations (i.e., at 0.43 ppm) in
12   this data set is challenging, because, in seven of the 19 European cities examined, the lowest 10% of the
13   CO distribution was at or above 2 mg/m^3 (1.74 ppm). Thus, the interpretation of the suggestive indication
14   of a threshold is limited.

15   In summary, the APHEA2 analysis of CO in 19 cities found an association between CO and total
16   and cardiovascular mortality in single-pollutant models, but the associations were substantially reduced
17   when NO_2 or BS was included in copollutant models. The evidence for potential confounding of CO risk
18   estimates by NO_2 is consistent with the findings from the NMMAPS and Canadian 12 cities studies. In
19   addition, Samoli et al. (2007) found that geographic region was a potential effect modifier, but such
20   geographic heterogeneity is not specific to CO, based on previously conducted APHEA studies. Finally,
21   examination of the CO concentration-response relationship found weak evidence of a CO threshold.

Other European Multi-City Studies

22   An additional European multi-city study was conducted by Biggeri et al. (2005) in eight Italian
23   cities. The authors examined the effect of short-term exposure to CO on mortality in single-pollutant
24   models using a time-series approach. In this analysis, because all of the pollutants showed positive
25   associations with the mortality endpoints examined and the correlations among the pollutants were not
26   presented, it is unclear if the observed associations are shared or confounded.

Summary of Multi-City Studies

27   In summary, the mortality risk estimates from single-pollutant models are comparable for the
28   NMMAPS and Canadian 12-city studies, 0.23 and 0.33, respectively, with the estimate from the APHEA2
29   study being slightly larger (0.57%) (Figure 5-15). In both the NMMAPS and Canadian studies, a 1-day
30   lag showed the strongest association; but the APHEA2 study used an a priori exposure window, the
31   average of 0- and 1-day lags, which has been found to be the exposure window most strongly associated
32   with mortality in PM analyses.

1   The APHEA2 risk estimates presented in Figure 5-15 are from a model that used a fixed amount of

2   smoothing to adjust for temporal confounding (8 df/yr), which is similar to that used in the NMMAPS

3   study (7 df/yr). However, the APHEA2 sensitivity analysis suggested an approximate 50 to 80%

4   difference in CO risk estimates between the models that used 8 or 12 df/yr, and the models that used

5   minimization of the absolute value of the sum of PACF of the residuals as a criterion to choose the

6   smoothing parameters. Thus, some model uncertainty likely influences the range of CO risk estimates

7   obtained from the studies evaluated.

8   The CO risk estimates from the aforementioned studies are also consistently sensitive to the

9   inclusion of NO_2 in a copollutant model (0.11, 0.03, and 0.26%, for the NMMAPS, Canadian 12-cities

10   study, and APHEA2, respectively). Thus, these results suggest confounding by NO_2. However, this

11   interpretation is further complicated because as with CO, NO_2 itself may be an indicator of combustion

12   sources, such as traffic. Because CO measurements tend to reflect more local impacts, due to the location

13   of monitors, than NO_2 (which is a secondary pollutant and therefore more spatially uniform) it is also

14   possible that CO, the less precisely measured pollutant in terms of spatial distribution, may "lose" in the

15   multipollutant model. Thus, it may not be accurate to interpret these results as evidence of "confounding

16   by NO_2."
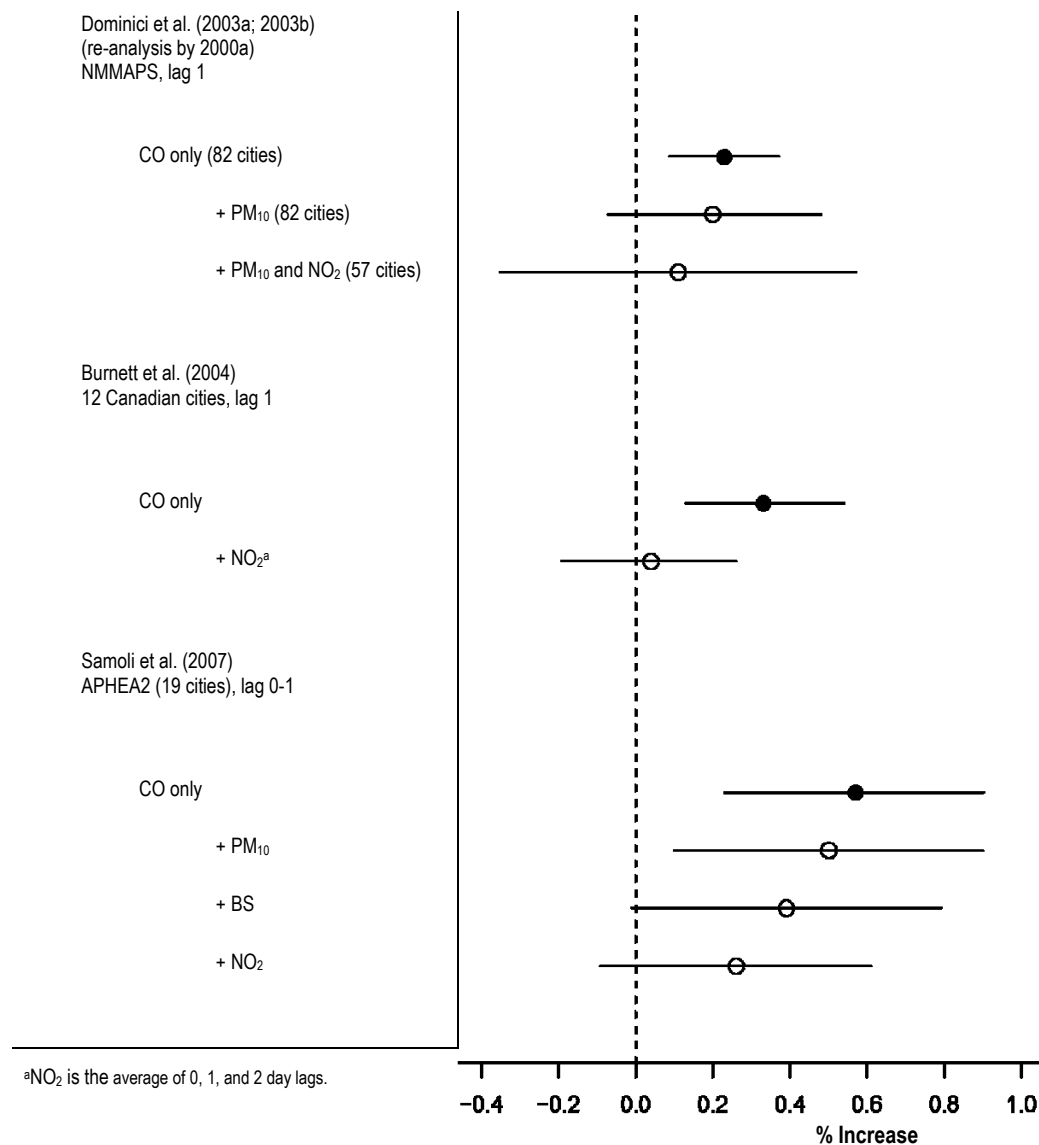
Figure 5-15. Summary of mortality risk estimates for short-term exposure to CO from multi-city studies. Estimates were standardized to 0.5 ppm and 0.75 ppm for studies that used 24-h avg CO and max 8-h avg CO exposure metrics, respectively.

5.6.1.3. Meta-Analysis of All Criteria Pollutants

1   Stieb et al. (2002) reviewed the time-series mortality studies published between 1985 and 2000,

2   and conducted a meta-analysis to estimate combined effects for PM_{10}, CO, NO_2, O_3, and SO_2. Because

3   many of the studies reviewed in the 2000 analysis used GAM with default convergence criteria,

4   Stieb et al. (2003) updated the estimates from the meta-analysis by separating the GAM versus non-GAM

5   studies. In this meta-analysis the authors also presented separate combined estimates for single- and

6   multipollutant models. Overall, there were more GAM estimates than non-GAM estimates for all of the

1   pollutants except SO_2. For CO, 4 single-pollutant model risk estimates were identified, resulting in a

2   combined estimate of 3.18% (95% CI: 0.76-5.66) per 0.5 ppm increase in 24-h avg CO, and only

3   1 multipollutant model risk estimate (0.00% [95% CI: -1.71 to 1.74]) from the non-GAM studies. Thus,

4   for CO, this study did not provide useful meta-estimates because the number of studies that contributed to

5   the combined estimates for CO was rather small.

5.6.1.4. Single-City Studies

6   In addition to the multi-city studies discussed above, there have also been several single-city U.S.-

7   and Canadian-based time-series mortality studies that examined CO. The single-city studies, similar to the

8   multi-city studies, often focused on the PM-mortality association, but also provided additional

9   information that is not available in the multi-city studies. Because the sample size used in each single-city

10   study is small, and subsequently results in wide confidence bands, a quantitative comparison of the results

11   from single- and multi-city studies is difficult. In addition, some studies do not present CO results

12   quantitatively adding to the inability to adequately compare studies. Table 5-17 lists the single-city studies

13   evaluated along with the mean CO concentrations reported in each study.

Table 5-17. **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)	New York, NY	1985-1994	24-h avg	2.45	95th: 4.04
Klemm et al. (2004)	Atlanta, GA	1998-2000	1-h max	1.31	Max: 7.40 75th: 1.66
Vedal et al. (2003)	Vancouver, BC, Canada	1994-1996	24-h avg	0.6	Max: 1.9 90th: 0.9
Villeneuve et al. (2003)	Vancouver, BC, Canada	1986-1999	24-h avg	1.0	Max: 4.9 90th: 1.6
Goldberg et al. (2003)	Montreal, Quebec, Canada	1984-1993	24-h avg	0.8	Max: 5.1 75th: 1.0
Hoek et al. (2000; 2001; Hoek, 2003)	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

[1] Study reported median CO concentrations.

Single-City Studies Conducted in the United States

14   De Leon et al. (2003) focused on the role of contributing respiratory diseases on the association

15   between air pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and primary non-respiratory mortality

1   (circulatory and cancer) in New York City, NY during the period 1985-1994. This study only presented

2   risk estimates graphically for each of the pollutants analyzed, except PM_{10}. In single-pollutant models,

3   PM_{10}, CO, SO_2, and NO_2 all showed the same pattern of association with circulatory mortality for

4   individuals ≥ 75, indicating a larger risk of death in individuals with contributing respiratory diseases

5   compared to those without. In two-pollutant models, PM_{10} and CO risk estimates were reduced, but each

6   remained significantly positive.

7   Klemm et al. (2004) analyzed 15 air pollutants for their associations with mortality in Atlanta, GA,

8   for a two-year period starting in August 1998. These pollutants included $PM_{2.5}$, $PM_{10-2.5}$, UFP surface area

9   and counts, aerosol acidity, EC, OC, SO_4^{2-}, O_3, CO, SO_2, and NO_2. This study presented risk estimates

10   using three levels of smoothing (quarterly, monthly, and biweekly knots) for temporal trend adjustment,

11   and suggested that the risk estimates were rather sensitive to the extent of smoothing. It should be noted

12   that temporal smoothing using biweekly knots is a more aggressive modeling approach than the degrees

13   of freedom approach used by most studies. In the single-pollutant models for all-cause mortality, the

14   strongest association, which was also statistically significant, was found for $PM_{2.5}$. CO, SO_4^{2-}, and $PM_{10-2.5}$

15   also showed positive associations with all-cause mortality, but they were not significant (CO: Quarterly

16   knots and Monthly Knots $\beta = 0.00002$ [SE = 0.00001]; Biweekly knots $\beta = 0.00001$ [SE = 0.00002]).

17   However, CO was significantly associated with circulatory mortality in older adults (≥ 65), and these

18   associations remained when $PM_{2.5}$ was included in the model (results were presented graphically).

Single-City Studies Conducted in Canada

19   Vedal et al. (2003) examined the association between short-term exposure to "low levels" of air

20   pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and daily morality in Vancouver, British Columbia, Canada

21   for the years 1994-1996. In this analysis, all of the risk estimates were presented graphically; however, the

22   results suggested that O_3 in the summer and NO_2 in the winter showed the strongest associations with

23   mortality. Vedal et al. (2003) found that CO was positively, but not significantly associated with mortality.

24   Additionally, the association between short-term exposure to NO_2 and mortality was found to be

25   consistent with the results from the Canadian multi-city study conducted by Burnett et al. (2004).

26   Villeneuve et al. (2003) also conducted an analysis using data from Vancouver, Canada, using a

27   cohort of 550,000 individuals whose vital status was ascertained between 1986 and 1999. In this study,

28   $PM_{2.5}$, $PM_{10–2.5}$, TSP, CoH, PM_{10}, SO_4^{2-}, O_3, CO, SO_2, and NO_2 were examined for their associations with

29   all-cause, cardiovascular, and respiratory mortality. When examining the association between gaseous

30   pollutants and all-cause mortality in this data set, NO_2 and SO_2 showed the strongest associations, while

31   the association between CO and all-cause mortality were generally weaker than those for NO_2 and SO_2.

32   For cardiovascular mortality, SO_2 risk estimates were smaller than those for NO_2 or CO, while for

33   respiratory mortality, SO_2 showed the strongest associations. However, the wider confidence bands of

1   these categories and the smaller daily counts make it difficult to assess CO associations with cause-

2   specific mortality outcomes.

3   Goldberg et al. (2003) contrasted associations between air pollution and mortality in individuals

4   with underlying CHF vs. mortality in individuals who were identified as having CHF one year prior to

5   death based on information from the universal health insurance plan in Montreal, Quebec, Canada, during

6   the period 1984-1993. In this study, Goldberg et al. (2003) examined associations between $PM_{2.5}$, CoH,

7   SO_4^{2-}, O_3, CO, SO_2, and NO_2, and mortality. The authors found no association between any of the air

8   pollutants and mortality with underlying CHF. However, Goldberg et al. (2003) found positive

9   associations between air pollution and mortality in individuals diagnosed with CHF one year prior to

10   death. Of the air pollutants examined, CoH, NO_2, and SO_2 were most consistently associated with

11   mortality for ages 65 and older, while CO showed positive but weaker associations compared to these

12   three pollutants.

Single-City Studies Conducted in Other Countries

13   Of the epidemiologic studies conducted in other countries that examine the association between

14   short-term exposure to CO and mortality only those studies conducted in European countries that have

15   CO levels comparable to the U.S. were evaluated. However, because Samoli et al. (2007) conducted a

16   multi-city study of European cities that focused on short-term exposure to CO, there are only a few

17   single-city studies that provide additional information, specifically those studies conducted in the

18   Netherlands. The Netherland studies were evaluated because they provide risk estimates for multiple

19   pollutants and cause-specific mortality, and consisted of relatively large sample sizes (i.e., the mortality

20   time-series of the entire country was analyzed).

21   Hoek et al. (2000) re-analyzed by (Hoek, 2003) examined associations between air pollution and

22   all-cause, cardiovascular, COPD, and pneumonia deaths in the entire Netherlands, the four major cities

23   combined, and the entire country minus the four major cities for the period 1986 to 1994. The air

24   pollutants analyzed included BS, PM_{10}, O_3, NO_2, SO_2, CO, SO_4^{2-} and NO_3^-. In the single-pollutant

25   models, all of the pollutants were significantly associated with all-cause mortality at lag 1-day and 0-

26   6 days when using the entire Netherlands data set. In the two-pollutant model, CO risk estimates were

27   reduced to null when PM_{10}, BS, SO_4^{2-} and NO_3^- were included in the model while the risk estimates for

28   these copollutants remained significantly positive. BS, CO, and NO_2 were highly correlated (r >0.85) in

29   this data set, and the authors noted "all these pollutants should be interpreted as indicators for motorized

30   traffic emissions" (Hoek et al., 2000). The authors found that O_3 showed the most consistent and

31   independent associations with mortality and that the risk estimates for all of the pollutants were

32   substantially higher in the summer months than in the winter months. Pneumonia deaths showed the

33   largest risk estimates for most pollutants including CO. The result from the Hoek et al. (2000) study is

34   somewhat in contrast to the result from the Samoli et al. (2007) multi-city study in that, in the Hoek et al.

1   (2000) analysis, CO was more sensitive to the addition of PM indices in copollutant models. This may be

2   due to the high correlation between CO and PM indices in the Netherlands.

3   Hoek et al. (2001) reanalysis by (Hoek, 2003) analyzed the Netherlands data using more specific

4   cardiovascular causes of death: MI and other IHD, arrhythmia, heart failure, cerebrovascular mortality,

5   and embolism/thrombosis. In this analysis, the authors analyzed O_3, BS, PM_{10}, CO, SO_2, and NO_2 in only

6   single-pollutant models. For all of the pollutants, risk estimates were larger for arrhythmia, heart failure,

7   and cerebrovascular mortality than for the combined cardiovascular mortality outcome. While the results

8   suggested larger impacts of air pollution on more specific cardiovascular causes, the authors did not

9   provide evidence of an association that was specific to any particular pollutant which would aid in

10   addressing the question of confounding.

Summary of Single-City Studies

11   Overall, it is difficult to identify a clear pattern of CO-mortality associations from the single-city

12   studies evaluated because of the relatively small sample sizes, expected variation in the air pollution mix

13   across cities, and differences in the analytical approaches used across studies. However, in all of these

14   studies, CO showed, at least to some extent, positive associations with all-cause or circulatory/

15   cardiovascular deaths. In addition the one study that examined specific cardiovascular causes of death

16   (Hoek et al., 2001)reanalysis by (Hoek, 2003) did not find an association that is specific to CO. Although

17   the extent of sensitivity of CO-mortality associations varied across studies, it could be attributed to the

18   likely variation in the correlation between CO and copollutants.

5.6.1.5. Summary of Mortality and Short-Term Exposure to CO

19   Among the gaseous pollutants examined in time-series mortality studies, CO is the least frequently

20   studied criteria air pollutant. Because CO was mostly treated as a potential confounder in these studies,

21   the information available regarding the nature of the association between short-term exposure to CO and

22   mortality is limited compared to the other pollutants. However, the recently available multi-city studies,

23   which consist of larger sample sizes, and single-city studies generally confirmed the findings reported in

24   the 2000 CO AQCD.

25   The multi-city studies which were evaluated, reported comparable CO mortality risk estimates for

26   total (non-accidental) mortality with the APHEA2 European multi-city study (Samoli et al., 2007)

27   showing slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when

28   examining potential confounding by copollutants these studies consistently showed that CO mortality risk

29   estimates were reduced when NO_2 was included in the model, but this observation may not be

30   "confounding" in the usual sense in that NO_2 may also be an indicator of other pollutants or pollution

31   sources (i.e., traffic).

1   Only one of the multi-city studies focused specifically on the CO-mortality association (Samoli et

2   al., 2007), the APHEA2 study), and in the process examined: (1) model sensitivity; (2) the CO-mortality

3   C-R relationship; and (3) potential effect modifiers of CO mortality risk estimates. The APHEA study

4   performed a sensitivity analysis, which indicated an approximate 50 - 80% difference in CO risk

5   estimates from a reasonable range of alternative models. In addition, the study examined the CO-mortality

6   concentration-response relationship through a grid search of varying threshold points, and found only

7   weak evidence of a CO threshold at 0.5 mg/m^3 (0.43 ppm), but this result was complicated by the lowest

8   10% of the CO distribution for seven of the 19 cities examined being at or above 2 mg/m^3 (1.74 ppm).

9   The examination of a variety of city-specific variables to indentify potential effect modifiers of the

10   CO-mortality relationship found that geographic region explained most of the heterogeneity in CO

11   mortality risk estimates with the CO-mortality associations being stronger in western and southern

12   European cities than eastern cities (Samoli et al., 2007). A similar pattern has been reported for black

13   smoke (BS) and SO_2 in previous APHEA studies, but the geographic variability observed does not

14   provide specific information, which could be used to evaluate the CO-mortality association.

15   The results from the single-city studies are generally consistent with the multi-city studies in that

16   some evidence of a positive association was found for mortality upon short-term exposure to CO.

17   However, the CO-mortality associations were often, but not always, attenuated when other copollutants

18   were included in the regression models. In addition, limited evidence was available to identify cause-

19   specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-term exposure to

20   CO.

21   The evidence from the recent multi- and single-city studies suggests that an association between

22   short-term exposure to CO and mortality exists, but limited evidence is available to evaluate cause-

23   specific mortality outcomes associated with CO exposure; and it is unclear if CO is acting alone or as an

24   indicator for other combustion-related pollutants. In addition, the results underscore the limitation of

25   current analytical methods to disentangle the health effects associated with one pollutant in the complex

26   air pollution mixture. Overall, the epidemiologic evidence **is suggestive of a causal relationship**

27   **between short-term exposure to relevant CO concentrations and mortality.**

5.6.2. Epidemiologic Studies with Long-Term Exposure to CO

28   The 2000 CO AQCD did not evaluate the association between long-term exposure to CO and

29   mortality because there were no studies at the time that examined this relationship. Since then there have

30   been several new studies that examined the association between long-term exposure to CO and mortality,

31   but it should be noted that these studies primarily focused on PM, and CO was only considered in these

1 studies as a potential confounder. Therefore, the information available from these new long-term exposure
2 studies is somewhat limited, especially in comparison to that for PM.

5.6.2.1. U.S. Cohort Studies

American Cancer Society Cohort Studies

3 Pope et al. (1995) investigated associations between long-term exposure to PM and mortality
4 outcomes in the ACS cohort. In this study, ambient air pollution data from 151 U.S. metropolitan areas in
5 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled
6 in the prospective study in 1982. Death outcomes were ascertained through 1989. $PM_{2.5}$ and SO_4^{2-} were
7 associated with total (non-accidental), cardiopulmonary, and lung cancer mortality, but not with mortality
8 for all other causes (i.e., non-accidental minus cardiopulmonary and lung cancer). Gaseous pollutants
9 were not analyzed in Pope et al. (1995). Jerrett et al. (2003) (using data from (Krewski et al., 2000)
10 conducted an extensive sensitivity analysis of the Pope et al. (1995). ACS data, augmented with
11 additional gaseous pollutants data. Due to the smaller number of CO monitors available compared to
12 SO_4^{2-}, the number of metropolitan statistical areas (MSAs) included in the CO analysis were reduced
13 (from 151 with SO_4^{2-}) to 107. The mean annual CO concentrations in these MSAs ranged from 0.19 to
14 3.95 ppm. CO was weakly negatively correlated with SO_4^{2-} ($r = -0.07$). Among the gaseous pollutants
15 examined (CO, NO_2, O_3, SO_2), only SO_2 showed positive associations with mortality, and in addition was
16 the only copollutant that reduced SO_4^{2-} risk estimates. For CO, the relative risk estimates for total (non-
17 accidental) mortality in single and copollutant models with SO_4^{2-} was 0.99 (95% CI: 0.96-1.01) and 0.98
18 (95% CI: 0.96-1.01), respectively, per 0.5 ppm increase in mean annual average CO concentrations.
19 Pope et al. (2002) conducted an extended analysis of the ACS cohort with double the follow-up
20 time (to 1998) and triple the number of deaths compared to the original Pope et al. (1995) study. In
21 addition to $PM_{2.5}$, data for all of the gaseous pollutants were retrieved for the extended period and
22 analyzed for their associations with mortality-specific outcomes. As in the 1995 analysis, the air pollution
23 exposure estimates were based on the MSA-level averages. The authors found that $PM_{2.5}$ and SO_4^{2-} were
24 both associated with total, cardiopulmonary, and lung cancer mortality.[1] In this study, the CO analysis
25 used two different data sets. The first data set consisted of 1980 data and 113 MSAs; while the second
26 data set used averages of the years 1982-1998 and 122 MSAs. The authors found, when using the 1980
27 data, that CO was not associated (risk estimates ~ 1) (See Figure 5-16) with all-cause, cardiopulmonary,
28 lung cancer, or mortality for all other causes. However, the analysis of the 1982-1998 data found that CO
29 was negatively (and significantly) associated with all-cause, cardio-pulmonary, and lung cancer mortality.
30 It is unclear why significant negative associations were observed when analyzing the 1982-1998 data, but

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[1] These results were presented graphically in Pope et al. (2002) and were estimated for Figure 5-16.

1 evidence from other mortality studies that examined the association between long-term exposure to CO

2 and mortality does not suggest that CO elicits a protective effect.

Women's Health Initiative Cohort Study

3 Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years

4 without previous CVD in 36 U.S. metropolitan areas from 1994 to 1998. They examined the association

5 between one or more fatal or nonfatal cardiovascular events and air pollutant concentrations. Exposures to

6 air pollution were estimated by assigning the annual mean levels of air pollutants measured at the nearest

7 monitor to the location of residence of each subject on the basis of its five-digit ZIP code centroid, which

8 allowed estimation of effects due to both within-city and between-city variation of air pollution. The

9 investigators excluded monitors whose measurement objective focused on a single point source or those

10 with "small measurement scale (0 to 100 meters)." Thus, presumably these criteria reduced some of the

11 exposure measurement error associated with monitors that are highly impacted by local sources.

12 During the course of the study, a total of 1,816 women had one or more fatal or nonfatal

13 cardiovascular events, including 261 cardiovascular-related deaths. Hazard ratios for the initial

14 cardiovascular event were estimated. The following results are for models that only included subjects

15 with non-missing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 CVD events). In

16 the single-pollutant models, $PM_{2.5}$ showed the strongest associations with CVD events among all

17 pollutants (HR = 1.24 [95% CI: 1.04-1.48] per 10-μg/m^3 increase in annual average), followed by SO_2

18 (HR = 1.07 [95% CI: 0.95-1.20] per 5-ppb increase in the annual average). For CO the single-pollutant

19 risk estimate was slightly (but not significantly) negative (HR = 0.96 [95%CI: 0.84-1.10]). In the

20 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

21 estimate was similar to the one presented in the single-pollutant model (HR = 0.96 [95% CI: 0.82-1.14]).

22 In addition, CO was not associated with CVD events in a single pollutant model (HR = 1.00 [95%CI:

23 0.90-1.10] per 0.5 ppm increase in mean annual average CO concentration) that used all available

24 observations. This study did not examine the correlations among pollutants and, therefore, the extent of

25 confounding could not be examined, but $PM_{2.5}$ was clearly the best predictor of cardiovascular events.

The Washington University-EPRI Veterans' Cohort Mortality Studies

26 Lipfert et al. (2000a) conducted an analysis of a national cohort of ~70,000 male U.S. military

27 veterans who were diagnosed as hypertensive in the mid 1970s and were followed for approximately 21

28 years (up to 1996). Demographically, 35% of the cohort consisted of African American men and 57% of

29 the cohort was defined as current smokers; however, 81% of the cohort had been smokers at one time in

30 their life. The study examined mortality effects in response to long-term exposure to multiple pollutants

31 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. (2000a) estimated

32 exposures by indentifying the county of residence at the time of entry to the study. Four exposure periods

1   (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three

2   most recent exposure periods were considered. The mean annual 95th percentile of hourly CO values

3   during these periods declined from 10.8 ppm to 2.4 ppm. The authors noted that the pollution risk

4   estimates were sensitive to the regression model specification, exposure periods, and the inclusion of

5   ecological and individual variables. Lipfert et al. (2000a) reported that indications of concurrent mortality

6   risks (i.e., associations between mortality and air quality for the same period) were found for NO_2 and

7   peak O_3. The estimated CO mortality risks were all negative, but not significant.

8   Lipfert et al. (2006b) examined associations between traffic density and mortality in the same

9   Veterans' Cohort, but in this analysis the follow-up period was extended to 2001. As in their 2000 study,

10   four exposure periods were considered but more recent years were included in the 2006 analysis. The

11   authors used the mean annual average of the 95th percentile of 24-h avg CO in each of the exposure

12   periods as the averaging metric. The traffic density variable was the most significant predictor of

13   mortality in their analysis, remaining so in two- and three pollutant models with other air pollutants

14   (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

15   risk estimates were not statistically significant for any of the other pollutants, except O_3. The natural log

16   of the traffic density variable (VKTA = vehicle-km traveled per year) was not correlated with CO

17   (r = -0.06), but moderately correlated with $PM_{2.5}$ (r = 0.50) in this data set. For the 1989-1996 data period,

18   the estimated mortality relative risk was 1.02 (95% CI: 0.98-1.06) per 1 ppm increase in the mean annual

19   95th percentile of hourly CO concentration in a single-pollutant model. The two-pollutant model, which

20   included the traffic density variable, resulted in a relative risk of 1.00 (95% CI: 0.96-1.04). Lipfert et al.

21   (2006b) note that the low risk estimates for CO in this study were consistent with those observed in other

22   long-term exposure studies, and may have been due to the localized nature of CO, which can lead to

23   exposure errors when data from centralized monitors is used to represent an entire county. Interestingly,

24   as Lipfert et al. (2006b) pointed out, the risk estimates due to traffic density did not vary appreciably

25   across these four periods even though regulated tailpipe emissions declined during the study period. The

26   authors speculated that some combination of other environmental factors such as road dust, psychological

27   stress, and noise (all of which constitute the environmental effects of vehicular traffic) along with spatial

28   gradients in SES might contribute to the non-negative effects observed.

29   Lipfert et al. (2006a) extended the analysis of the Veterans Cohort data to include the EPA's

30   Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. The authors

31   analyzed the STN data for the year 2002, and again used county-level averages. In addition, they analyzed

32   $PM_{2.5}$ and gaseous pollutants data for 1999 through 2001. As in the other Lipfert et al. (2006b) study,

33   traffic density was the most important predictor of mortality, but associations were also observed for EC,

34   vanadium (V), nickel (Ni), and NO_3^-. Ozone, NO_2, and PM_{10} also showed positive, but weaker

35   associations. The authors found no association between the mean annual 95th percentile of hourly CO

1   values and mortality (RR = 0.995 [95% CI: 0.988-1.001] per 1 ppm increase in CO concentration) in a

2   single-pollutant model. The study did not present multipollutant model results for CO.

Endpoint	Reference	Cohort	Years of Mortality Data	Year(s) of AQ Data
	Pope et al. (2002)[a]	ACS	1982-1998	1980
	Pope et al. (2002)[a]	ACS	1982-1998	1982-1998
	Lipfert et al. (2006b)	Veterans	1976-2001	1976-2001
All-cause	Lipfert et al. (2006b)	Veterans	1976-2001	1976-2001
	Lipfert et al. (2006a)	Veterans	1997-2001	1999-2001
	Jerrett et al. (2003)	ACS	1982-1998	1982-[c]
	Jerrett et al. (2003)	ACS	1982-1998	1982-[c]
Cardio-pulmonary	Pope et al. (2002)[a]	ACS	1982-1998	1980
	Pope et al. (2002)[a]	ACS	1982-1998	1982-1998
Cardiovascular	Miller et al. (2007)[b]	WHI	1994-1998	2000
	Miller et al. (2007)[b]	WHI	1994-1998	2000

[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).
[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] Natural log of vehicle-km traveled per year (VKTA).

Figure 5-16.   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

1   An ecological cross-sectional analysis involves regressing county- (or city) average health outcome
2   values on county-average explanatory variables such as air pollution and census statistics. Unlike the
3   cohort studies described above, to the extent that individual level confounders are not adjusted for, the
4   cross-sectional study design is considered to be subject to ecologic confounding. However, all of the
5   cohort studies described above are also semi-ecologic in that the air pollution exposure variables are
6   ecologic (Kuenzli and Tager, 1997). In this sense, cross-sectional studies may be useful in evaluating the
7   correlation among exposure variables.

8   Lipfert and Morris (2002) conducted ecological cross-sectional regressions for U.S. counties
9   (except Alaska) during five periods: 1960-1969, 1970-1974, 1979-1981, 1989-1991, and 1995-1997. They
10   regressed age-specific (15-44, 45-64, 65-74, 76-84, and 85+) all-cause (excluding AIDS and trauma)
11   mortality on air pollution, demography, climate, SES, lifestyle, and diet. The authors analyzed TSP, PM_{10},
12   $PM_{2.5}$, SO_4^{2-}, SO_2, CO, NO_2, and O_3. However, air pollution data was only available for limited periods of
13   time depending on the pollutant: TSP up to 1991; PM_{10} between 1995 and 1999; and $PM_{2.5}$ between
14   1979-1984 and 1999. In response to the varying number of counties with valid air pollution data by
15   pollutant and time, Lipfert and Morris (2002) employed a staged regression approach. In the first stage, a
16   national model was developed for each dependent variable, excluding air pollution variables. In the
17   second stage, regressions were performed with the residuals on concurrent and previous periods' air
18   pollution variables to identify the pollutants of interest. Overall, there were too many results to summarize
19   because of the large number of age groups, lagged exposure time windows, and mortality study periods
20   examined in the study, but similar to the ACS cohort studies, $PM_{2.5}$ and SO_4^{2-} were found to be
21   consistently and positively associated with mortality. Lipfert and Morris (2002) generally found the
22   strongest associations in the earlier time periods, and when mortality and air quality were measured in
23   different periods (e.g., mortality data 1995-1997 and CO data 1970-1974). Also, consistent with the
24   Lipfert et al. (2000a) and the Pope et al. (2002) cohort studies, CO was frequently negatively (and often
25   significantly) associated with mortality in older age groups, especially when mortality was matched with
26   CO levels in more recent time periods. The younger age group (15-44) often showed a positive
27   association with CO, but considering the small number of deaths attributed to this age group (less than
28   1% of total deaths), the association was not informative. Overall, this study highlighted that the
29   CO-mortality associations presented in purely ecologic study designs are generally consistent with those
30   found in semi-individual cohort studies.

5.6.2.3. Summary of Mortality and Long-Term Exposure to CO

1   The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD (2000) that
2   investigated the association between long-term exposure to CO and mortality consistently found null or
3   negative mortality risk estimates. No such studies were discussed in the 2000 CO AQCD. The re-analysis
4   of the ACS data (Pope et al., 1995) by Jerrett et al. (2003) found no association between long-term
5   exposure to CO and mortality. Similar results were obtained in an updated analysis conducted by Pope
6   et al. (2002) when using earlier (1980) CO data, but negative associations were found when using more
7   recent (1982-1998) data. The Women's Health Initiative (WHI) Study also found no association between
8   CO and CVD events (including mortality) using the data from recent years (1994-1998) (Miller et al.,
9   2007), while the series of Veterans Cohort studies found no association or a negative association between
10   mean annual 95th percentile of hourly CO values and mortality (Lipfert et al., 2006a; Lipfert et al.,
11   2006b). One additional study was identified that used a cross-sectional study design, Lipfert and Morris
12   (2002), which reported results for a study of U.S. counties that are generally consistent with the cohort
13   studies: positive associations between long-term exposure to $PM_{2.5}$ and SO_4^{2-} and mortality, and generally
14   negative associations with CO. Overall, the consistent null and negative associations observed across
15   epidemiologic studies which included cohort populations encompassing potentially susceptible
16   subpopulations (i.e., post-menopausal women and hypertensive men) combined with the lack of evidence
17   for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and the
18   absence of a proposed mechanism to explain the progression to mortality following long-term exposure to
19   CO provide supportive evidence that is **suggestive of no causal relationship between long-term**
20   **exposure to CO and mortality.**

5.7. Public Health Impacts

21   This section addresses several issues relating to the broader public health impact from exposure to
22   ambient CO through a discussion on: (1) the shape of the concentration-response (C-R) relationship for
23   CO, which is based primarily on controlled human exposure studies; and (2) the identification of
24   subpopulations which may experience increased risks from CO exposures, through either enhanced
25   susceptibility (e.g., as a result of pre-existing disease, genetic factors, age) and/or vulnerability associated
26   with external factors or differential exposure (e.g., altitude, close proximity to sources, activity patterns).

5.7.1. Concentration-Response Relationship

1   Currently, very limited information is available in the human clinical and epidemiologic literature
2   regarding the CO C-R relationship and the potential presence of a CO threshold. Two human clinical
3   studies described in the 2000 CO AQCD had evaluated the C-R relationship between CO and onset of
4   exercise-induced angina among individuals with CAD, but at the high end of CO concentrations (i.e., CO
5   levels above the current NAAQS). Anderson et al. (1973) exposed 10 adult men with stable angina for 4 h
6   to CO concentrations of 50 and 100 ppm, which resulted in average COHb levels of 2.9% and 4.5%,
7   respectively. Both exposures significantly decreased the time to onset of exercise-induced angina relative
8   to room air control (1.6% COHb). However, there was no difference in response between the two
9   exposure concentrations of CO. In a much larger study, 63 adults with stable angina were exposed for 1 h
10   to two concentrations of CO (average exposure concentrations of 117 and 253 ppm) resulting in average
11   pre-exercise COHb levels of 2.4% and 4.7% (Allred et al., 1989). Relative to control (average COHb
12   0.7%), COHb levels of 2.4% and 4.7% were observed to decrease the time to onset of angina by 4.2%
13   ($p = 0.054$) and 7.1% ($p = 0.004$), respectively. In addition, these investigators reported a statistically
14   significant decrease in the time to exercise-induced ST-segment depression with increasing COHb levels.
15   These findings provide some evidence of a significant C-R relationship at COHb concentrations between
16   2.4 and 4.7%. However, the human clinical literature has yet to evaluate the C-R relationship at lower CO
17   concentrations or COHb levels.
18   One study in the epidemiologic literature attempted to examine the C-R relationship at the low end
19   of CO concentrations through a threshold analysis. Samoli et al. (2007) in their examination of the
20   association between short-term exposure to CO and mortality conducted an ancillary analysis to examine
21   the potential presence of a CO threshold. In this analysis the authors compared city-specific models to the
22   threshold model, which consisted of thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007)
23   then computed the deviance between the two models and summed the deviances for a given threshold
24   over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest
25   threshold examined), the comparison with the linear no-threshold model indicated weak evidence
26   (p-value >0.9) for a threshold. However, determining the presence of a threshold at the very low range of
27   CO concentrations (i.e., at 0.43 ppm) in this data set is challenging, because, in seven of the 19 European
28   cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m^3 (1.74 ppm). By only
29   using the 12 cities in the analysis that had minimum CO concentrations approaching 0.5 mg/m^3
30   (0.43 ppm), a limited number of observations were examined around the threshold of interest, which
31   subsequently contributed to the inability to draw conclusions regarding the potential presence of a
32   threshold with any certainty.

5.7.2. Potentially Susceptible and Vulnerable Populations

1   Interindividual variation in human responses to air pollutants indicates that not all individuals
2   exposed to pollutants respond similarly. That is, some subpopulations are at increased risk to the
3   detrimental effects of pollutant exposure. The NAAQS are intended to provide an adequate margin of
4   safety for both general populations and susceptible and vulnerable subpopulations, or those subgroups
5   potentially at increased risk for ambient air pollution health effects. For the purposes of this document, a
6   susceptible subpopulation is defined as one with an intrinsic biological characteristic (e.g., disease) that
7   might result in an adverse health effect at pollutant concentrations below those needed to elicit the same
8   response in the general population, or result in a more adverse effect at the same concentration. A
9   vulnerable subpopulation is one with a non-biological characteristic (e.g., differential exposure, living at
10   altitude) that results in increased incidence of health effects from an ambient pollutant relative to the
11   general population. The previous review of the CO NAAQS identified certain groups within the
12   population that may be more susceptible to the effects of CO exposure, including individuals (particularly
13   older adults) with CAD and other vascular diseases, anemia patients, patients with obstructive lung
14   disease, and infants. Other subgroups considered to be somewhat vulnerable in the previous review
15   include individuals living at altitude and those using certain medications that can increase endogenous CO
16   production. Tables 5-18 and 5-19 provide an overview of the characteristics that contribute to susceptible
17   and vulnerable subpopulations, respectively, which have been observed in the examination of the NAAQS
18   for all criteria pollutants. Those characteristics of susceptible/vulnerable subpopulations exposed
19   specifically to CO, as mentioned in the literature that encompasses this ISA, are discussed below.

Table 5-18.   Characteristics of susceptible subpopulations.

Susceptibility Characteristics[1]
Pre-existing disease: Cardiovascular diseases, Anemia, Obesity, Diabetes, Respiratory diseases (e.g., asthma, obstructive lung disease)
Age: Children, Older Adults (65+)
Infants: Premature, Low Birth Weight
Gender
Pregnancy
Birth Defects
Race/Ethnicity
Genetic Factors
Nutritional status

[1] Susceptible (i.e., intrinsic) refers to biological characteristics of an individual, which can include life stage, genetics, and pre-existing disease.

Table 5-19. Characteristics of vulnerable subpopulations.

Vulnerability Characteristics[1]
Altitude
Level of Exercise
Proximity to Roadways
Medication Use
Geographic Location
Work Environment (e.g., outdoor workers)
Air Conditioning Use
SES
Education Level
Nutritional status

[1] Vulnerable (i.e., extrinsic) refers to non-biological variables associated with an individual that can result in a health effect.

5.7.2.1. Susceptibility Characteristics

Cardiovascular Disease

1 Individuals with heart disease may be at a greater risk from CO exposure since they may already
2 have compromised O_2 delivery. CO is notable among air pollutants because it is especially harmful in
3 individuals with impaired cardiovascular systems. Persons with a normal cardiovascular system can
4 tolerate substantial concentrations of CO, if they vasodilate in response to the hypoxemia produced by
5 CO. In contrast, individuals unable to vasodilate in response to CO exposure may show evidence of
6 ischemia at low concentrations of COHb. Many of the controlled human exposure studies have focused
7 on individuals with IHD.

8 An estimated 81 million American adults (1 in 3) have one or more type of cardiovascular disease
9 (CVD), with an estimated 47% of these being 60 or more years of age. CVD is the leading cause of death
10 in the U.S. with nearly 2,400 deaths each day-an average of one death every 37 seconds (Rosamond et al.,
11 2008). For the major diseases within the category of total CVD, about 73 million Americans have high
12 BP, 16 million have CHD, 5 million have heart failure, 5 million have stroke, and the estimated
13 prevalence of congenital cardiovascular defects is estimated to be between 650,000 to 1.3 million
14 (Rosamond et al., 2008). In the U.S., IHD is the largest major killer, causing 1 in 5 deaths. Because the
15 numbers of affected people are so high, even relatively small percent increases in cardiovascular mortality
16 or morbidity in the population could have a large impact on public health.

17 Each year in the U.S. approximately 780,000 people experience a new or recurrent stroke, with the
18 majority of these being a first stroke (77%). On average this equates to someone in the U.S. having a
19 stroke every 40 seconds with a death occurring every 3 to 4 minutes. When considered separately from

1   other CVDs, stroke ranks third among all causes of death, behind diseases of the heart and cancer

2   (Rosamond et al., 2008). While epidemiologic evidence is weak regarding associations between ambient

3   CO and stroke, diseased individuals could exhibit increased sensitivity to CO exposure.

Obstructive Lung Disease

4   Patients with obstructive lung disease, such as COPD, were identified as a susceptible

5   subpopulation in the 2000 CO AQCD. COPD is a progressive disease resulting in decreased air flow to

6   the lungs, and is especially prevalent among smokers. A majority of COPD patients have exercise

7   limitations as demonstrated by a decrease in O_2 saturation during mild to moderate exercise. This makes

8   individuals with hypoxia resulting from COPD particularly sensitive to CO during submaximal exercise

9   typical of normal daily activity. COPD patients who are smokers may have baseline COHb levels of

10   4-8%, leaving little reserve for increases in COHb due to ambient exposure. COPD is often accompanied

11   by a number of changes in gas exchange, including increased V_D and V/Q inequality (Marthan et al.,

12   1985), which could slow both CO uptake and elimination. Patients with pulmonary sarcoidosis may have

13   a decrease in lung volumes, a loss of D_LCO, and gas exchange abnormalities during exercise, including

14   decreased P_aO_2 and increased alveolar-arterial oxygen pressure difference (Lamberto et al., 2004). A

15   controlled human exposure study on 19 individuals with COPD (Bathoorn et al., 2007) found that two of

16   the patients experienced COPD exacerbation during or following CO exposure at 100-125 ppm for 2 h,

17   although a slight anti-inflammatory effect was also observed. The few epidemiologic studies that

18   evaluated the relationship between ambient CO and increased hospital admissions or ED visits for COPD

19   show weak positive associations. Epidemiologic results were similar for asthmatics, who can also

20   experience exercise-induced airflow limitation.

Anemia

21   Health status can influence the toxicity involved with CO exposure by influencing the severity of

22   hypoxia resulting from CO exposure. Any condition that would alter the blood O_2 carrying capacity or

23   content will result in a greater risk from COHb induced hypoxia and decreased tissue O_2 delivery. The

24   severity of this effect depends upon the initial level of hypoxia. Anemias are a group of diseases that

25   result in insufficient blood O_2 or hypoxia due to Hb deficiency through hemolysis, hemorrhage, or

26   reduced hematopoiesis. Anemia may result from pathologic conditions characterized by chronic

27   inflammation such as malignant tumors or chronic infections (Cavallin-Stahl et al., 1976a, b). The bodies

28   of people with anemia compensate causing cardiac output to increase as both heart rate and stroke volume

29   increase. The endogenous production of CO, thus COHb, is increased in patients with hemolytic anemia

30   due to increased heme catabolism, causing an increased baseline COHb concentration. One of the most

31   prevalent anemias arises from a single-point mutation of Hb, causing sickle cell diseases. The Hb affinity

32   for O_2 and O_2 carrying capacity is reduced causing a shift to the right in the O_2 dissociation curve. It is

1 well documented that African-American populations have a higher incidence of sickle cell anemia, which
2 may be a risk factor for CO hypoxia.
3   Any disturbance in RBC hemostasis by acceleration of destruction of hemoproteins will lead to
4 increased production of CO. Pathologic conditions such as anemias, hematomas, thalassemia, Gilbert's
5 syndrome with hemolysis, and other hematological diseases and illness will accelerate CO production
6 (Berk et al., 1974; Hampson, 2007; Meyer et al., 1998; Solanki et al., 1988). Patients with hemolytic
7 anemia exhibit COHb levels 2- to 3-times higher than healthy individuals and CO production rates 2- to
8 8-times higher (Coburn et al., 1966).

Age and Gender

9   Age and gender alter the variables that influence the uptake, distribution, and elimination of CO.
10 COHb levels decline more rapidly in young children than adults after CO exposure (Joumard et al., 1981;
11 Klasner et al., 1998). After infancy, the COHb half-life increases with age, practically doubling between 2
12 and 70 years (Joumard et al., 1981). The rate of this decrease in CO elimination is very rapid in the
13 growing years (2 to 16 years of age), but slows beyond adolescence. Alveolar volume and D_LCO
14 increased with increasing body length of infants and toddlers (Castillo et al., 2006), suggesting a further
15 degree of lung development and faster CO uptake. After infancy, increasing age decreases D_LCO and
16 increases V_A/Q mismatch, causing it to take longer to both load and eliminate CO from the blood (Neas
17 and Schwartz, 1996).
18   COHb concentrations are generally lower in female subjects than in male subjects (Horvath et al.,
19 1988) and the COHb half-life is longer in healthy men than in women of the same age, which may be
20 partially explained by differences in muscle mass or the slight correlation between COHb half-life and
21 increased height (Joumard et al., 1981). The rate of decline of D_LCO with age is lower in middle-aged
22 women than in men; however, it evens out towards older age (Neas and Schwartz, 1996). Women also
23 tended to be more resistant to altitude hypoxia (Horvath et al., 1988).

Newborns and Young Infants

24   Fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure, making it
25 difficult to estimate fetal COHb based on maternal levels. Human fetal Hb has a higher affinity for CO
26 than adult Hb (Di Cera et al., 1989). Maternal and fetal COHb concentrations have been modeled as a
27 function of time using a modified CFK equation (Hill et al., 1977). At steady-state conditions, the fetal
28 COHb is up to 10% higher than the maternal COHb levels, for example, exposure to 30 ppm CO results
29 in a maternal COHb of 5% and a fetal COHb of 5.5%. The fetal CO uptake lags behind the maternal for
30 the first few hours but later may overtake the maternal values. Similarly, during washout, the fetal COHb
31 levels are maintained for longer, with a half-life of around 7.5 hours versus the maternal half-life of
32 around 4 hours. In addition, women experience fluctuating COHb levels during pregnancy as well as

1   through the menstrual cycle when endogenous CO production doubles in the progesterone phase

2   (Delivoria-Papadopoulos et al., 1974; Mercke and Lundh, 1976).

3   Epidemiologic studies of birth outcomes have examined well-established clinical metrics of infant

4   health. Preterm birth (PTB, <37 weeks gestation) and low birth weight (LBW, birth weight <2,500 g)

5   have been established as strong predictors of infant mortality and morbidity (Barker et al., 2002;

6   Berkowitz and Papiernik, 1993; Li et al., 2003; McIntire et al., 1999). In 2004, 36.5 percent of all infant

7   deaths in the U.S. were preterm-related (MacDorman et al., 2007). Vital statistics for the year 2005 in the

8   U.S. showed that the rate for PTB was 12.7%, which has risen 20% since 1990, and the rate for LBW was

9   8.2%, which has risen 17% since 1990 (Martin et al.).

10   Congenital anomalies remain the leading cause of infant death in the U.S. (Martin et al.). In 2004,

11 for every 1,000 live births in the U.S. the infant (up to 1 year of age) mortality rate was 6.8 deaths, while

12 the neonatal (under 28 days of age) mortality rate was 4.5 deaths, and the postneonatal (between 28 days

13 and 1 year of age) mortality rate was 2.4 deaths (National Center for Health Statistics, 2007). From 1968

14 to 1995, the proportion of infant mortality attributable to birth defects increased from 14.5% to 22.2 %

15 (Centers for Disease Control and Prevention, 1998). Limited epidemiologic research has been conducted

16 on congenital anomalies because of their rare occurrence, which makes it difficult to detect small effects

17 within defined exposure periods. For example, in 2005 the rates for spina bifida and anencephaly in the

18 U.S. were 18.0 and 11.3 per 100,000 births respectively (Martin et al., 2007) and as a result of folic acid

19 fortification the prevalence of these defects declined considerably from 1995 to 2002 (Williams et al.,

20 2005). Survival rate among infants with spina bifida had also improved due to folic acid fortification (Bol

21 et al., 2006). The rate of cleft lip/palate is higher at approximately 79.1 per 100,000 births (Martin et al.,

22 2007).

23   The rate of cardiovascular defects is much higher. Data from the Metropolitan Atlanta Congenital

24 Defects Program (MACDP), which is one of the most comprehensive birth defect registries in the U.S.,

25 showed that the prevalence of congenital heart defects had increased between 1968 and 1997. During

26 1995-1997 the rate was 90.2 per 10,000 births (0.9%) and this had increased from 58.7 per 10,000 births

27 since 1986-1972 (Botto et al., 2001). Cardiovascular defects are the single largest contributor to infant

28 mortality attributable to birth defects (Centers for Disease Control and Prevention, 1998). Between 1979

29 and 1997, 1 in 10 infant deaths (9.8%) was associated with a congenital heart defect, and 1 in 13 infant

30 deaths (7.4%) was due to a congenital heart defect (Boneva et al., 2001).

5.7.2.2. Vulnerability Characteristics

Altitude

31   Increased altitude changes a number of factors that contribute to the uptake and elimination of CO.

32 The relationship between altitude and CO exposure has been discussed in depth in the 2000 CO AQCD

1   and other documents (U.S. EPA, 1978). In an effort to maintain proper O_2 transport and supply,

2   physiological changes occur as compensatory mechanisms to combat the decreased barometric pressure

3   and resulting altitude induced HH (HH). HH, unlike CO hypoxia, causes humans to hyperventilate, which

4   reduces arterial blood CO_2 (hypocapnia) and increases alveolar partial pressure of O_2. Hypocapnia will

5   lead to difficulty of O_2 dissociation and decreased blood flow, thus reducing tissue O_2 supply. HH

6   increases BP and cardiac output and leads to redistribution of blood from skin to organs and from blood to

7   extravascular compartments. Generally these changes will favor increased CO uptake and COHb

8   formation, as well as CO elimination. In hypoxic conditions both CO and O_2 bind reduced Hb through a

9   competitive-parallel reaction (Chakraborty et al., 2004). Breathing CO (9 ppm) at rest at altitude produced

10   higher COHb compared to sea level (McGrath et al., 1993), whereas high altitude exposure with exercise

11   caused a decrease in COHb levels versus similar exposure at sea level (Horvath et al., 1988). This

12   decrease could be a shift in CO storage or suppression of COHb formation, or both. Altitude also

13   increases the baseline COHb levels by inducing endogenous CO production. Early HH increased lung

14   HO-1 protein and activity, whereas chronic HH induced endogenous CO production in nonpulmonary

15   sites (see Section 4.5) (Carraway et al., 2000).

16   As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation,

17   polycythemia or increased red blood cell count, and increased tissue capillarity and Mb content in skeletal

18   muscle, which could also favor increased CO uptake. Most of the initial adaptive changes gradually revert

19   to sea level values. However, differences in people raised at high altitude persist even after

20   reacclimatization to sea level (Hsia, 2002).

21   Altitude has been shown to be positively associated with baseline COHb concentrations (McGrath,

22   1992; McGrath et al., 1993). This increase in COHb with altitude induced hypoxia has also been

23   associated with increases in the mRNA, protein, and activity of HO-1 in rats and cells leading to

24   enhanced endogenous CO production (Carraway et al., 2002; Chin et al., 2007). Whether other variables

25   (such as an accelerated metabolism or a greater pool of Hb, transient shifts in body stores, or a change in

26   the elimination rate of CO) play a role has not been explored.

Activity Patterns

27   Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in

28   gas exchange. O_2 consumption can increase more than 10 fold during exercise. Similarly, ventilation,

29   membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase

30   proportional to work load. The majority of these changes facilitate CO uptake and transport, by increasing

31   gas exchange efficiency.

32   The COHb elimination rate decreases with physical activity (Joumard et al., 1981). Healthy

33   subjects exposed to CO and achieving COHb levels of approximately 4-5% observed a significant

34   detriment to exercise duration and maximal effort capability (measured by metabolic equivalent units)

1 (Adir et al., 1999). It is possible that CO lowers the anaerobic threshold, allowing earlier fatigue of the
2 skeletal muscles and decreased maximal effort capability.

Proximity to Roadways

3 Individuals that spend a substantial amount of time on or near heavily traveled roadways, such as
4 commuters and those living or working near freeways, are likely to experience elevated CO
5 concentrations, as discussed in Chapter 3, and therefore constitute a potentially vulnerable subpopulation
6 due to differential exposure. Studies of commuters have shown that commuting time is an important
7 predictor of CO exposure for those traveling by car, cycling, and walking, and that on-road CO
8 concentrations are typically two to five times higher than concentrations measured at the roadside.

Medication Use

9 Not all endogenous CO production is derived from Hb breakdown. Other hemoproteins, such as
10 Mb, cytochromes, peroxidases, and catalase, contribute 20-25% to the total amount of endogenous CO
11 (Berk et al., 1976). All of these sources result in a blood COHb concentration between 0.4 and 0.7%
12 (Coburn et al., 1965). This baseline level of endogenous production can be altered by drugs or a number
13 of physiological conditions that alter RBC destruction, other hemoprotein breakdown, or bilirubin
14 production. Nicotinic acid (Lundh et al., 1975), allyl-containing compounds (acetamids and barbiturates)
15 (Mercke et al., 1975b), diphenylhydantoin (Coburn, 1970b), progesterone (Delivoria-Papadopoulos et al.,
16 1974), and contraceptives (Mercke et al., 1975a) will increase CO production. Compounds such as carbon
17 disulfide and sulfur-containing chemicals (parathion and phenyltiourea) will increase CO by acting on
18 P450 system moieties (Landaw et al., 1970). The P450 system may also cause large increases in CO
19 produced from the metabolic degradation of dihalomethanes leading to very high (>10%) COHb levels
20 (Manno et al., 1992), which can be further enhanced by prior exposure to HCs or ethanol (Pankow et al.,
21 1991; Wirkner and Poelchen, 1996). HO can catalyze the release of CO from the auto-oxidation of
22 phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers
23 et al., 1994).
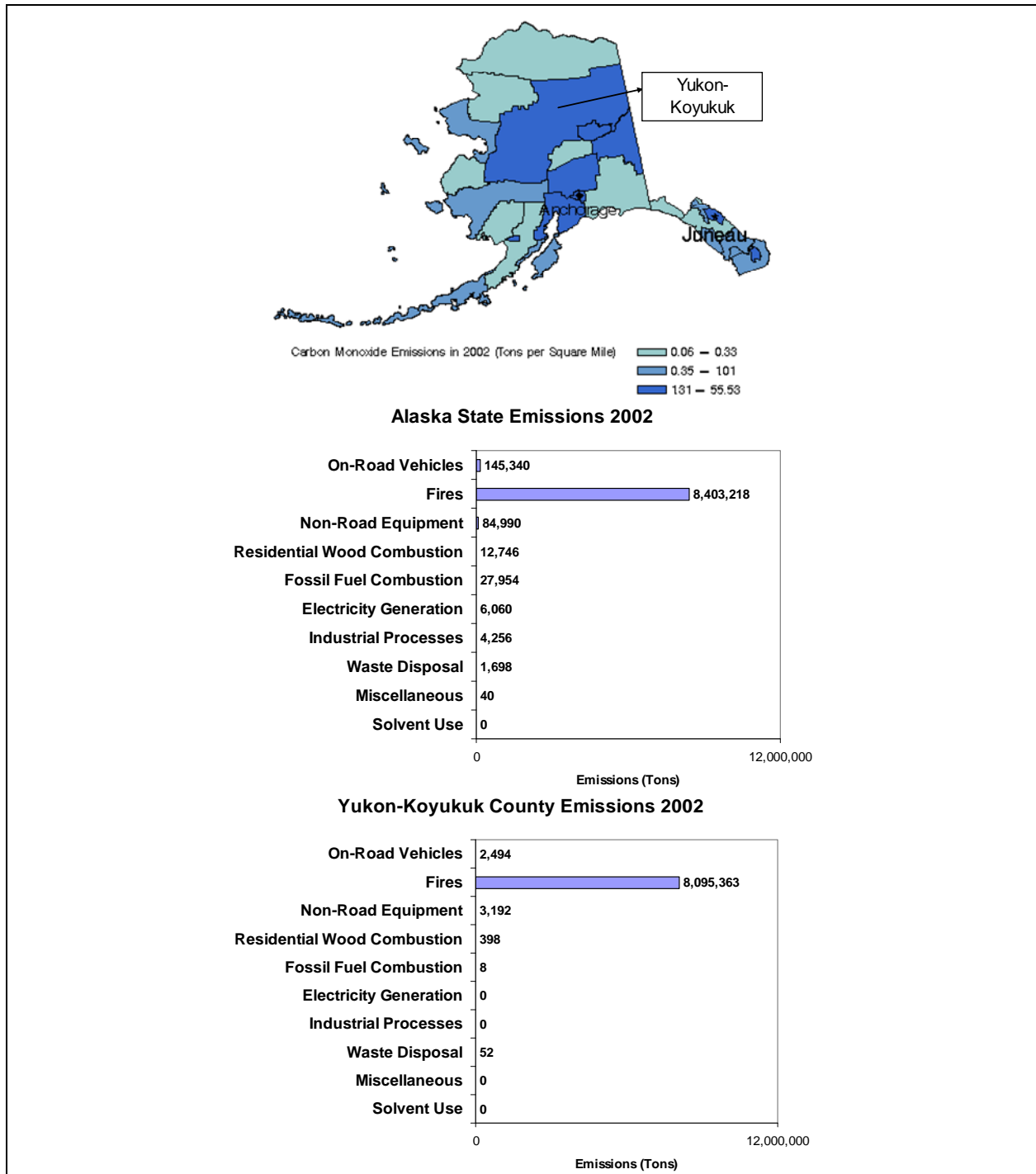
Annex A. Atmospheric Science

Alaska State Emissions 2002

Category	Emissions (Tons)
On-Road Vehicles	145,340
Fires	8,403,218
Non-Road Equipment	84,990
Residential Wood Combustion	12,746
Fossil Fuel Combustion	27,954
Electricity Generation	6,060
Industrial Processes	4,256
Waste Disposal	1,698
Miscellaneous	40
Solvent Use	0

Yukon-Koyukuk County Emissions 2002

Category	Emissions (Tons)
On-Road Vehicles	2,494
Fires	8,095,363
Non-Road Equipment	3,192
Residential Wood Combustion	398
Fossil Fuel Combustion	8
Electricity Generation	0
Industrial Processes	0
Waste Disposal	52
Miscellaneous	0
Solvent Use	0

Figure A-1. CO emissions density map and distribution for the state of Alaska and for Yukon-Koyukuk County in Alaska.
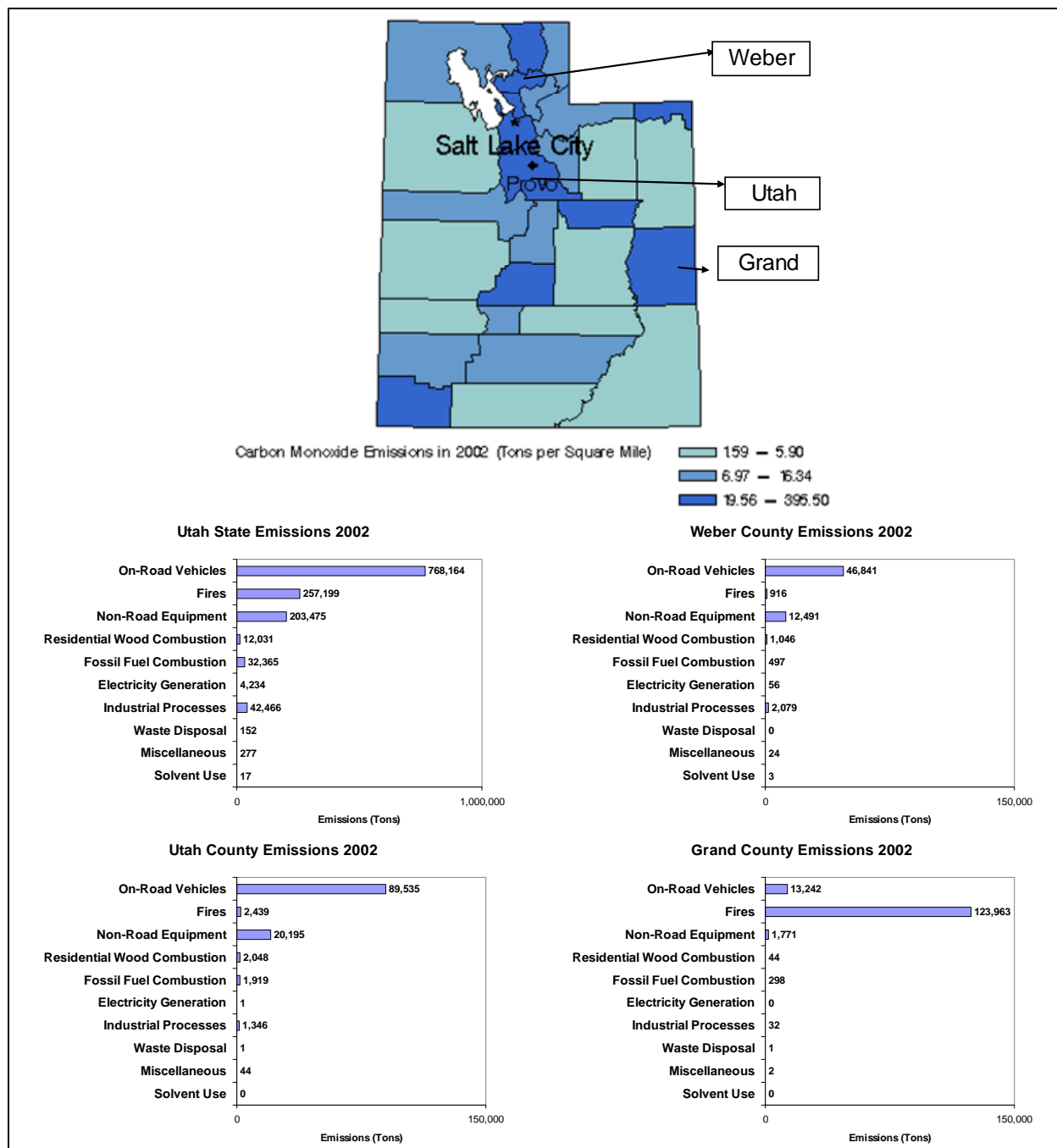
Figure A-2. CO emissions density map and distribution for the state of Utah and for selected counties in Utah.
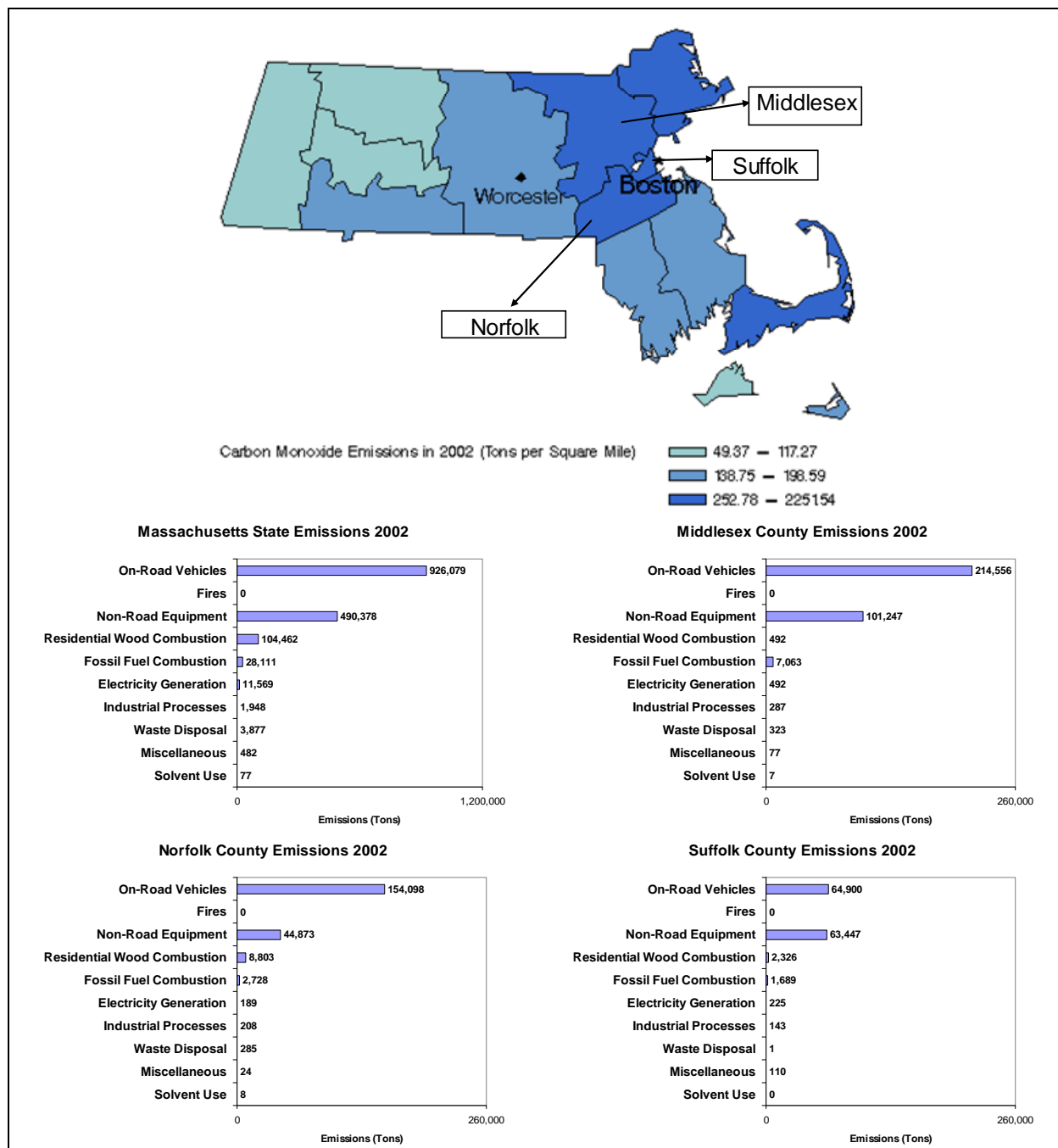
Figure A-3. CO emissions density map and distribution for the state of Massachusetts and for selected counties in Massachusetts.
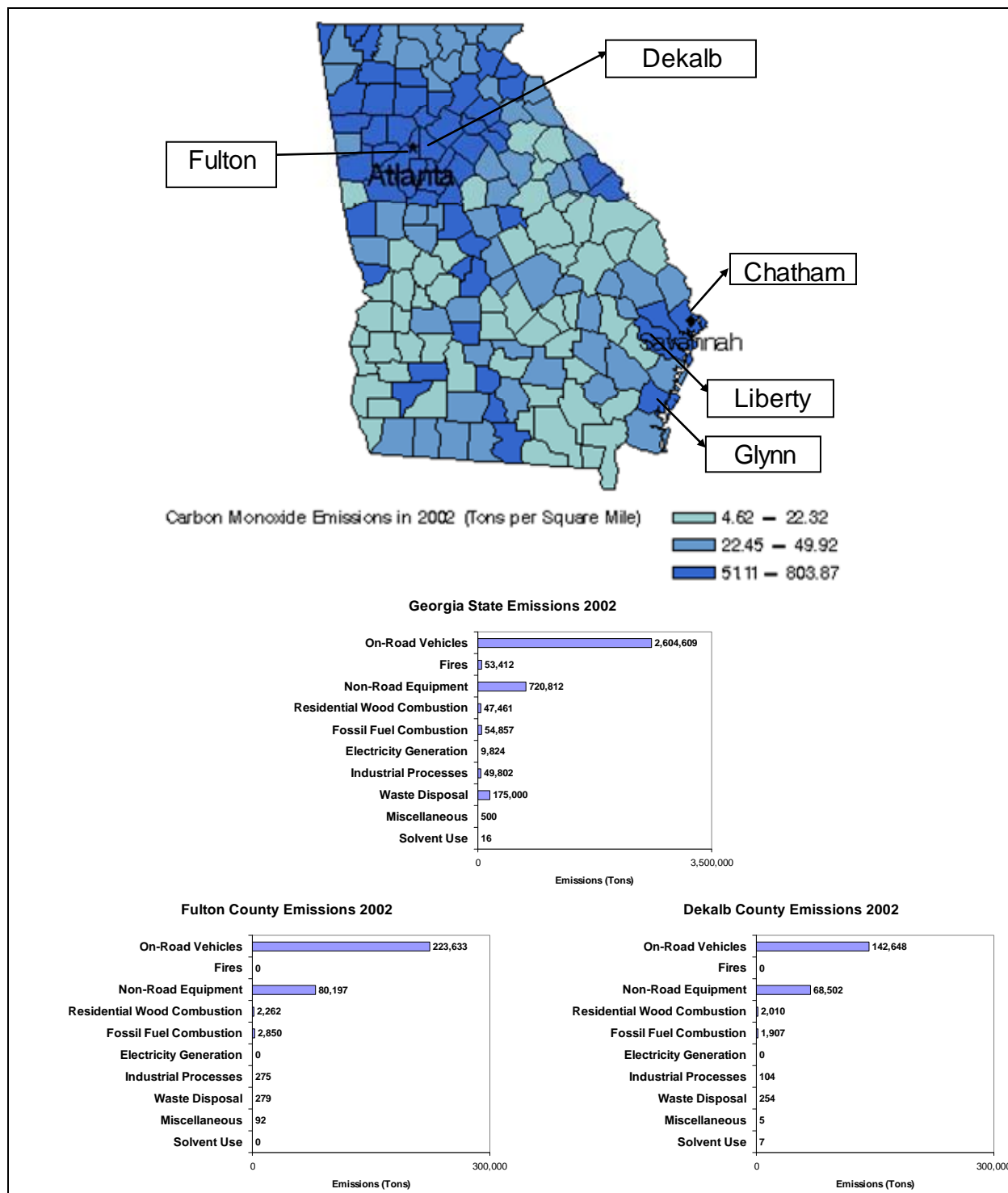
Figure A-4a. CO emissions density map and distribution for the state of Georgia and for selected counties in Georgia (1 of 2).
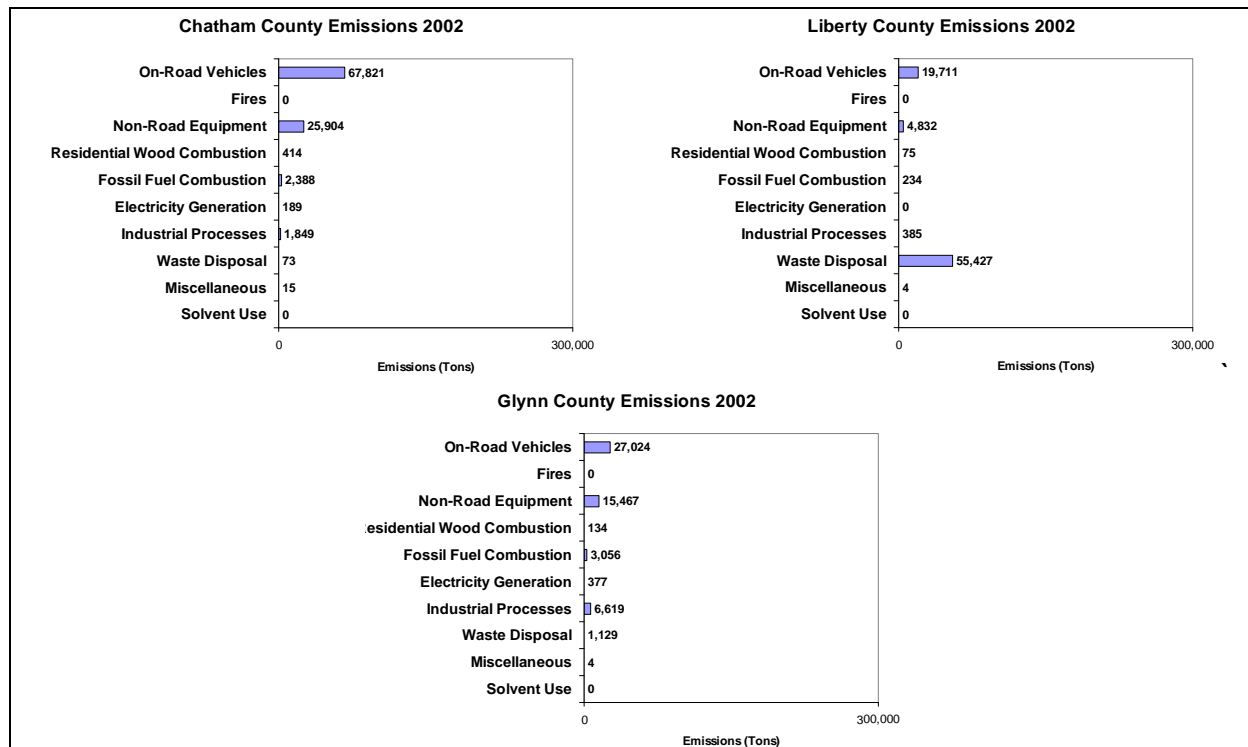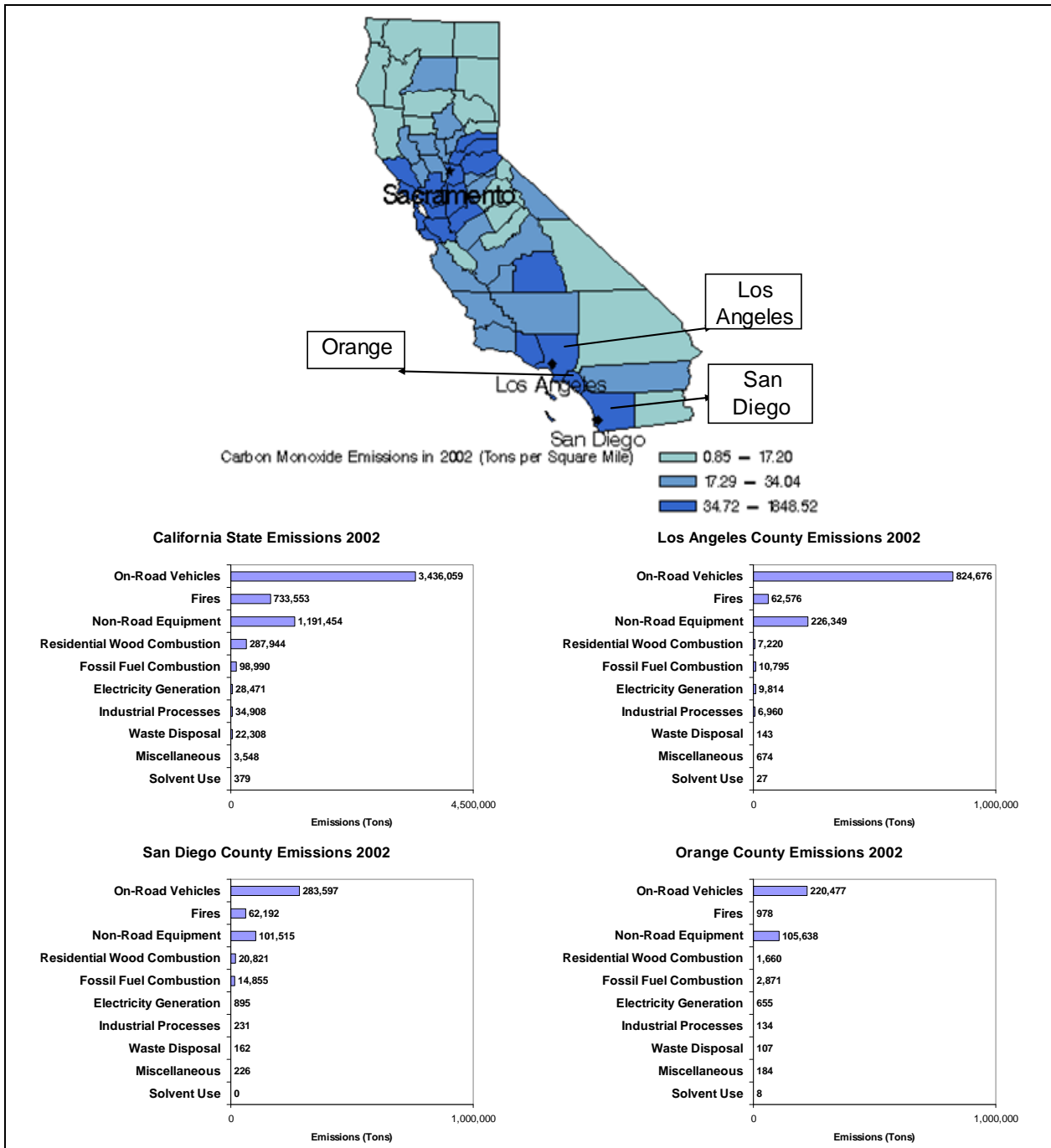
Chatham County Emissions 2002

Category	Emissions (Tons)
On-Road Vehicles	67,821
Fires	0
Non-Road Equipment	25,904
Residential Wood Combustion	414
Fossil Fuel Combustion	2,388
Electricity Generation	189
Industrial Processes	1,849
Waste Disposal	73
Miscellaneous	15
Solvent Use	0

Liberty County Emissions 2002

Category	Emissions (Tons)
On-Road Vehicles	19,711
Fires	0
Non-Road Equipment	4,832
Residential Wood Combustion	75
Fossil Fuel Combustion	234
Electricity Generation	0
Industrial Processes	385
Waste Disposal	55,427
Miscellaneous	4
Solvent Use	0

Glynn County Emissions 2002

Category	Emissions (Tons)
On-Road Vehicles	27,024
Fires	0
Non-Road Equipment	15,467
Residential Wood Combustion	134
Fossil Fuel Combustion	3,056
Electricity Generation	377
Industrial Processes	6,619
Waste Disposal	1,129
Miscellaneous	4
Solvent Use	0

Figure A-4b.   CO emissions distribution for selected counties in Georgia (2 of 2).

Figure A-5. CO emissions density map and distribution for the state of California and for selected counties in California.
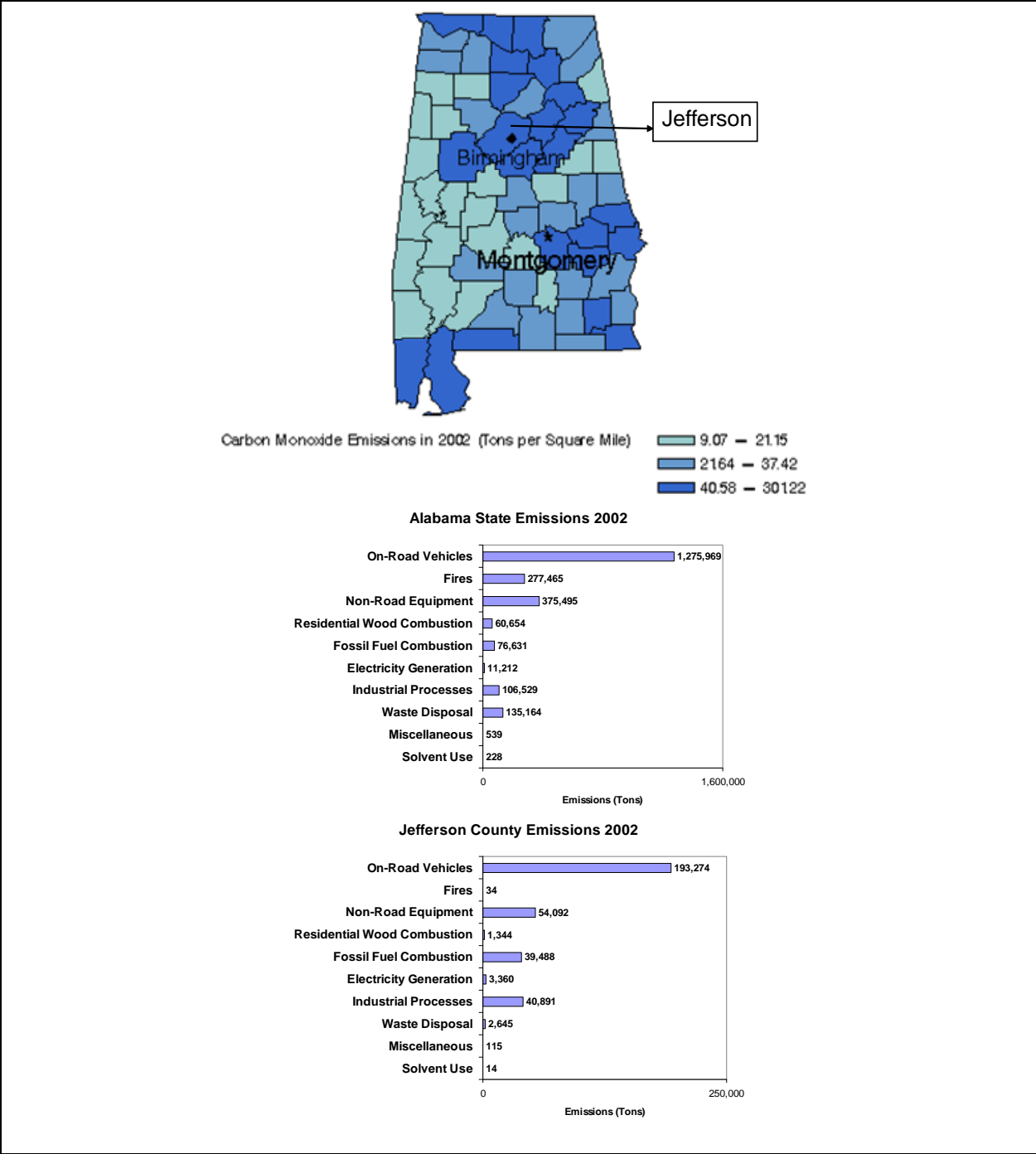
Figure A-6. CO emissions density map and distribution for the state of Alabama and for Jefferson County in Alabama.
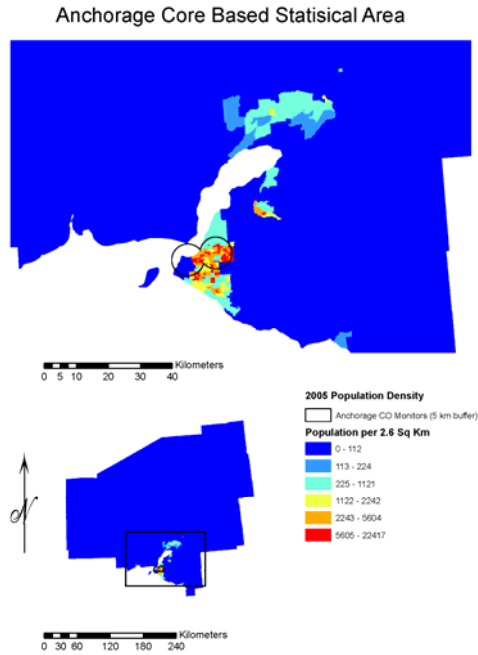
Figure A-7. Map of CO monitor locations with respect to population density in the Anchorage CBSA, total population.
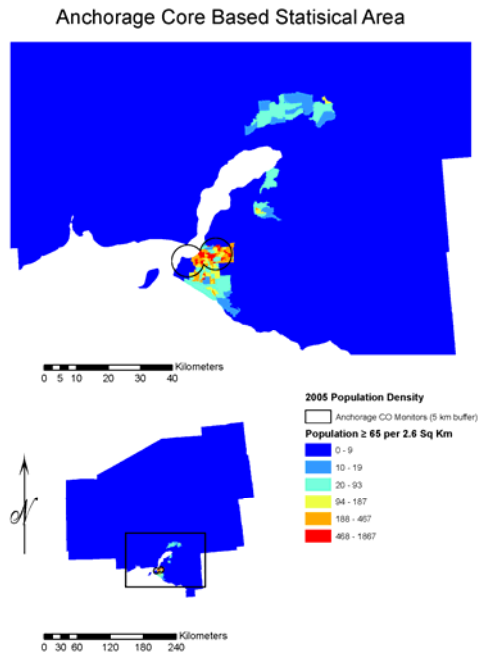

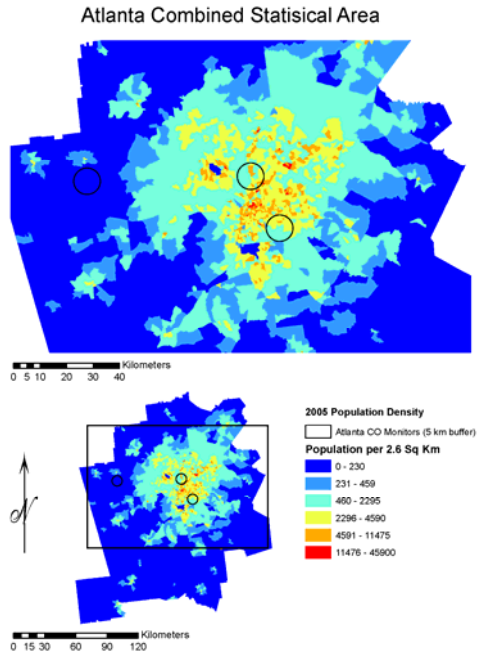**Figure A-8.** Map of CO monitor locations with respect to population density in the Anchorage CBSA, ages 65 and older.

Figure A-9. Map of CO monitor locations with respect to population density in the Atlanta CSA, total population.
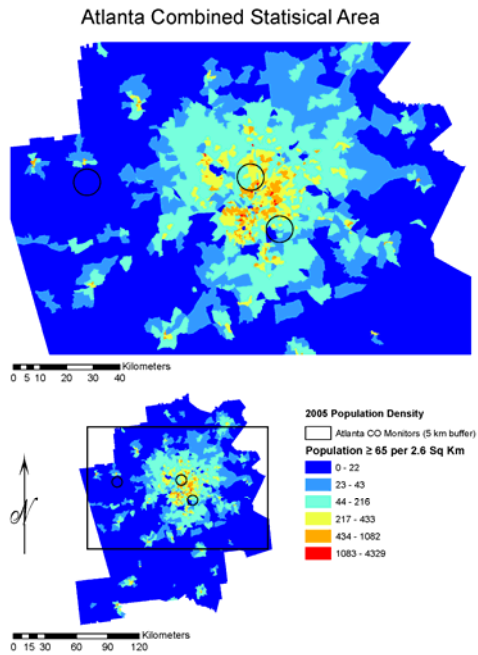
Figure A-10. Map of CO monitor locations with respect to population density in the Atlanta CSA, ages 65 and older.
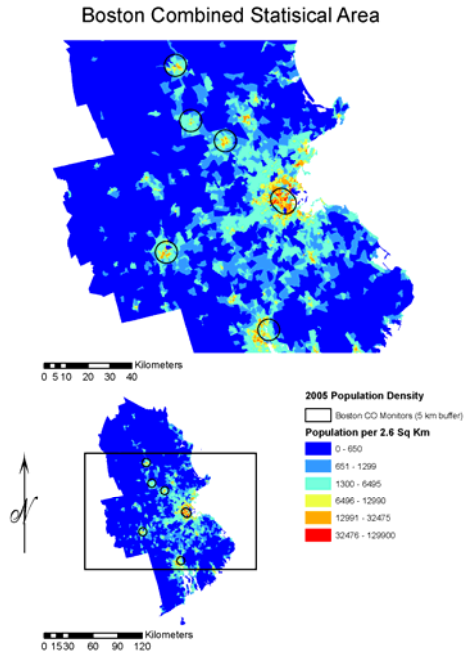
Figure A-11. **Map of CO monitor locations with respect to population density in the Boston CSA, total population.**
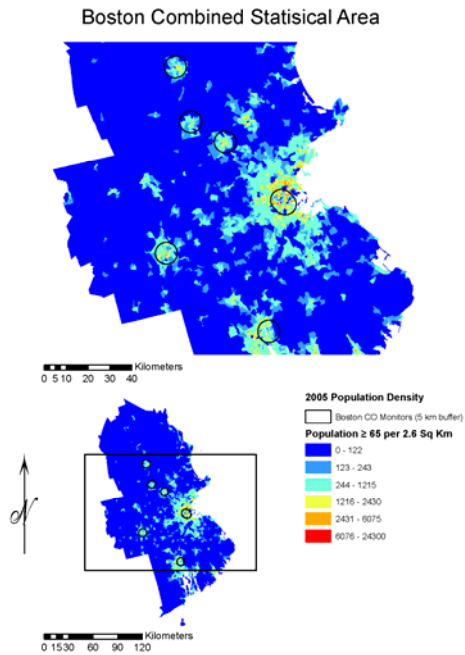

Figure A-12. **Map of CO monitor locations with respect to population density in the Boston CSA, ages 65 and older.**
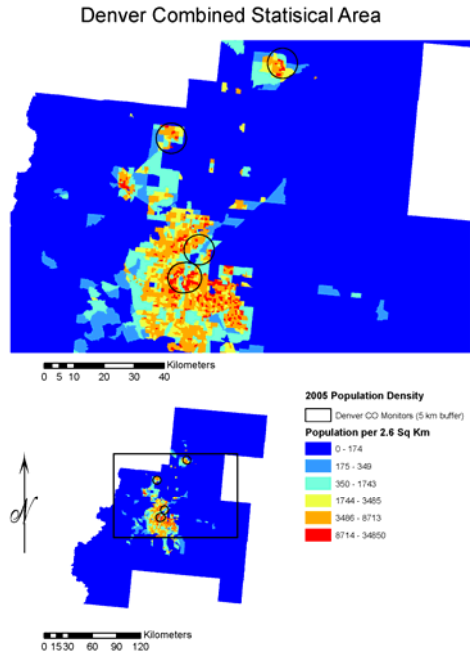
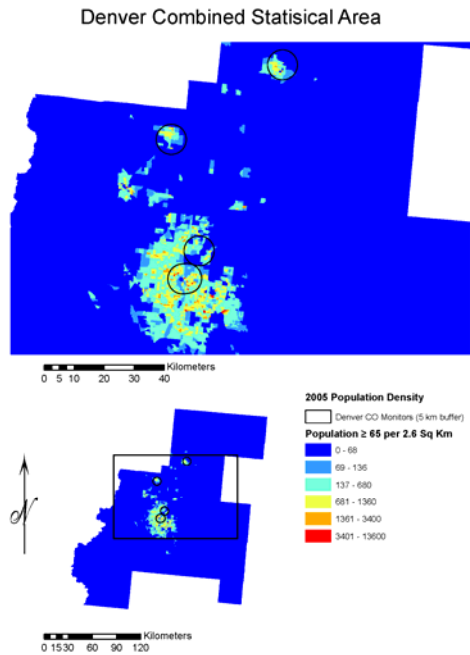**Figure A-13.** **Map of CO monitor locations with respect to population density in the Denver CSA, total population.**

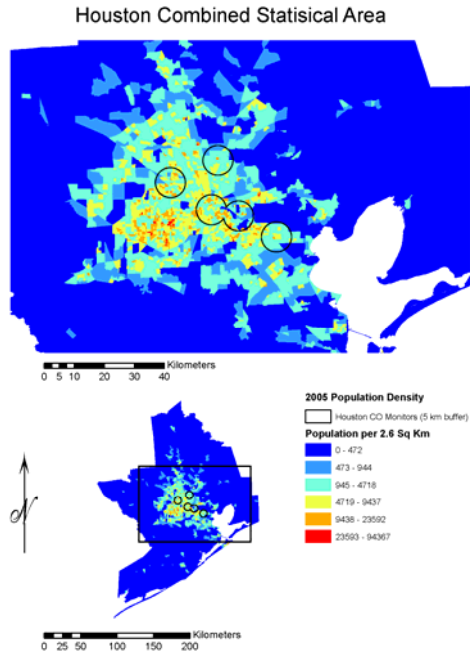**Figure A-14.** **Map of CO monitor locations with respect to population density in the Denver CSA, ages 65 and older.**

Figure A-15. Map of CO monitor locations with respect to population density in the Houston CSA, total population.
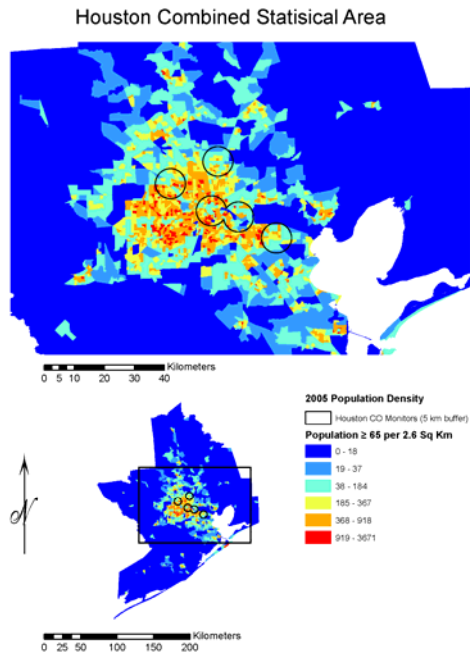

Figure A-16. Map of CO monitor locations with respect to population density in the Houston CSA, ages 65 and older.

Figure A-17. Map of CO monitor locations with respect to population density in the Los Angeles CSA, total population.

Figure A-18. Map of CO monitor locations with respect to population density in the Los Angeles CSA, ages 65 and older.

Figure A-19.   Map of CO monitor locations with respect to population density in the New York City CSA, total population.

Figure A-20.   Map of CO monitor locations with respect to population density in the New York City CSA, ages 65 and older.
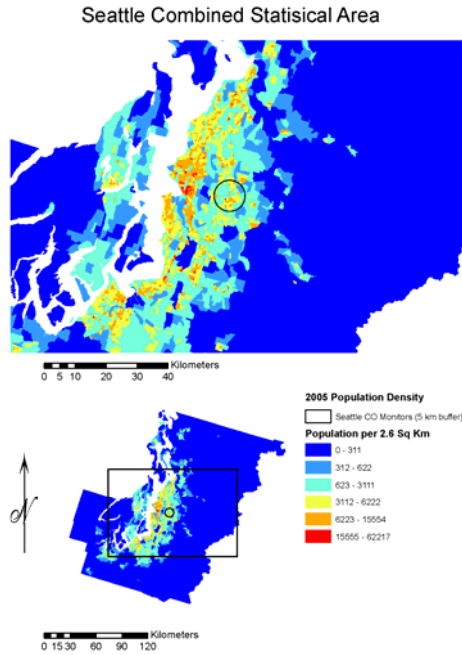
Figure A-21. **Map of CO monitor locations with respect to population density in the Seattle CSA, total population.**
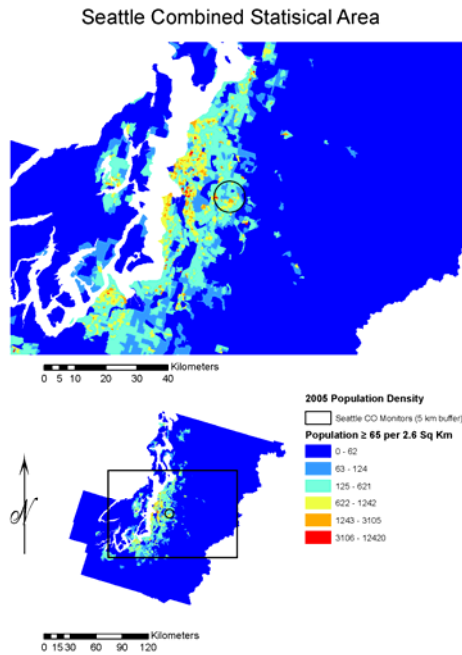
Figure A-22. **Map of CO monitor locations with respect to population density in the Seattle CSA, ages 65 and older.**
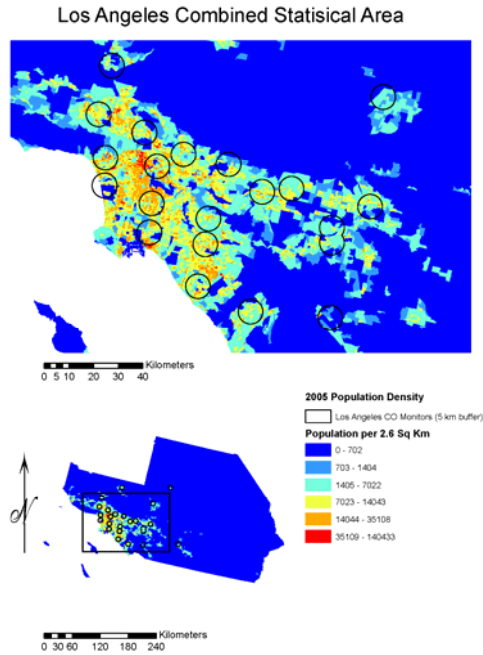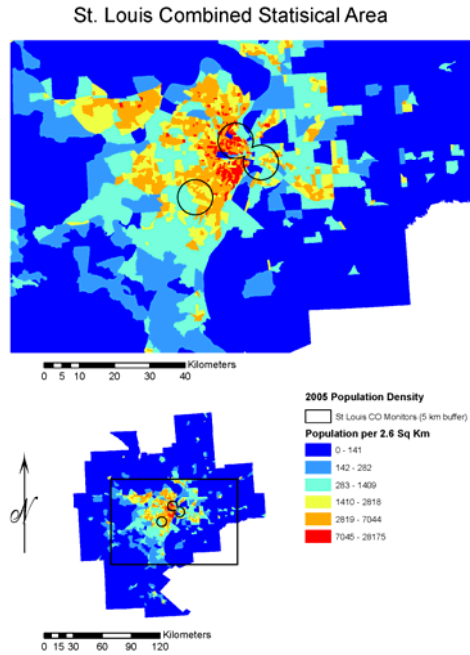
Figure A-23. Map of CO monitor locations with respect to population density in the St. Louis CSA, total population.
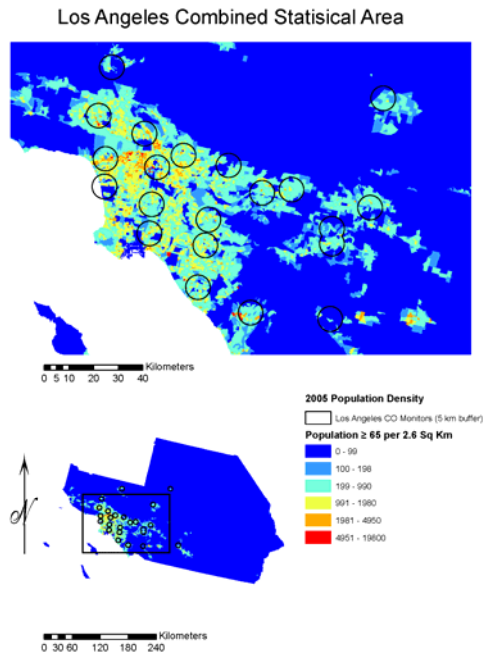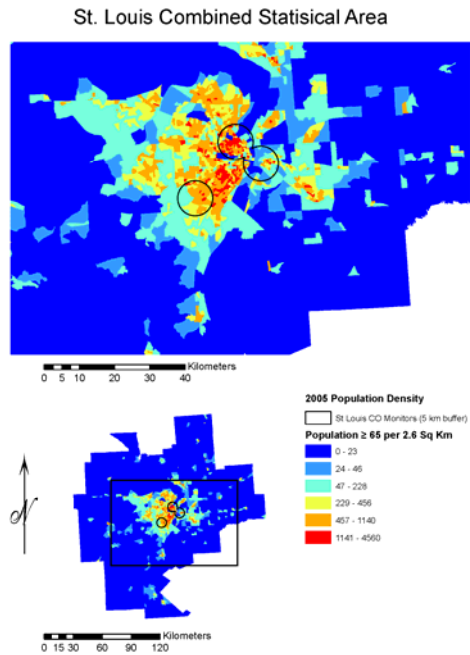

Figure A-24. Map of CO monitor locations with respect to population density in the St. Louis CSA, ages 65 and older.
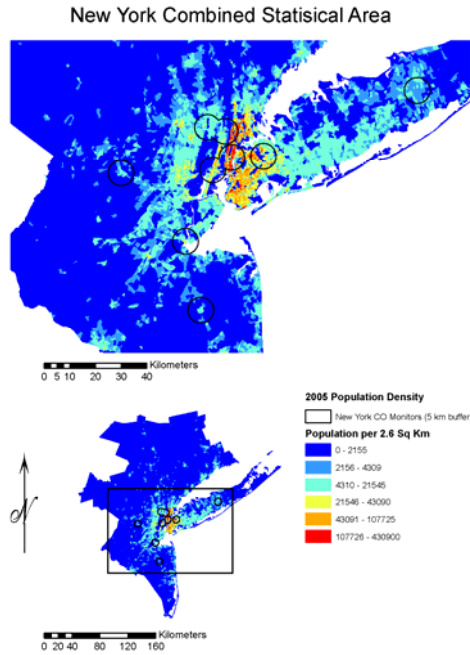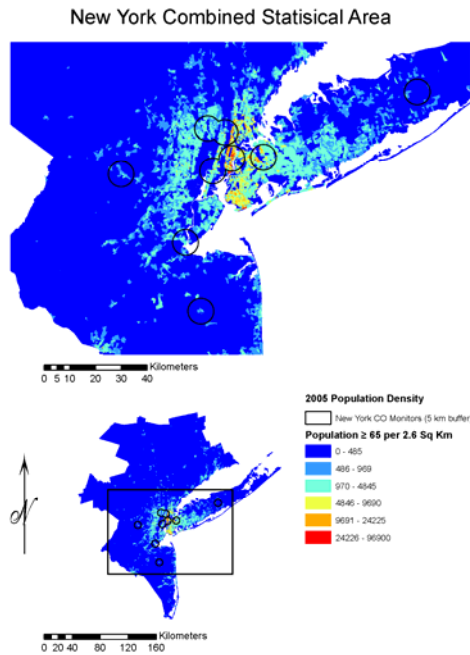
Figure A-25.   Map of CO monitor locations with AQS Site IDs for Anchorage, AK.

Table A-1.   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.

	Anchorage	
	A	**B**
A	1.00	0.73
	0.0	1.1
	0.00	0.32
	0.0	9.0
	Legend	
B	r	1.00
	P90	0.0
	COD	0.00
	d	0.0

	A	B
Mean	1.04	1.10
Obs	12969	12703
SD	0.94	1.04

Figure A-26. **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.**

Atlanta Combined Statistical Area

Figure A-27.   Map of CO monitor locations with AQS Site IDs for Atlanta, GA.

Table A-2.   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.

Atlanta

		A	B	C
A		1.00	0.60	0.12
		0.0	0.5	0.7
		0.00	0.27	0.37
		0.0	22.5	74.7
B			1.00	0.10
			0.0	0.7
			0.00	0.38
	Legend		0.0	61.7
C	r			1.00
	P90			0.0
	COD			0.00
	d			0.0

Figure A-28. 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.
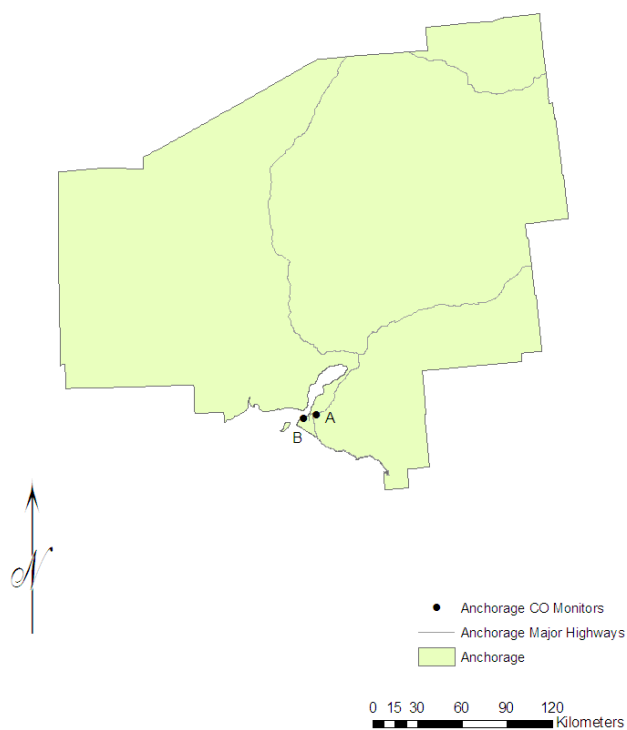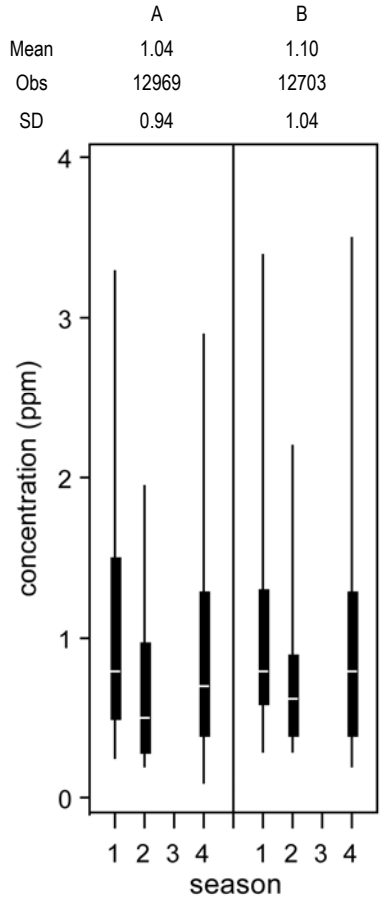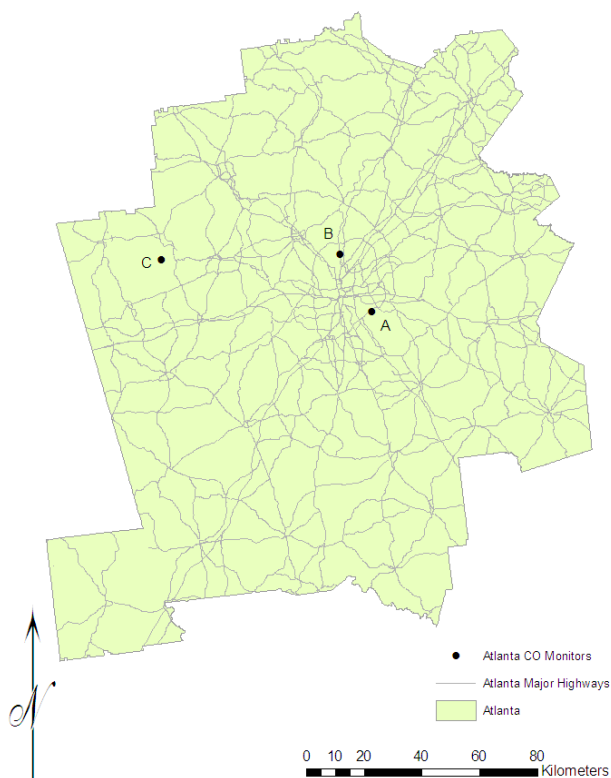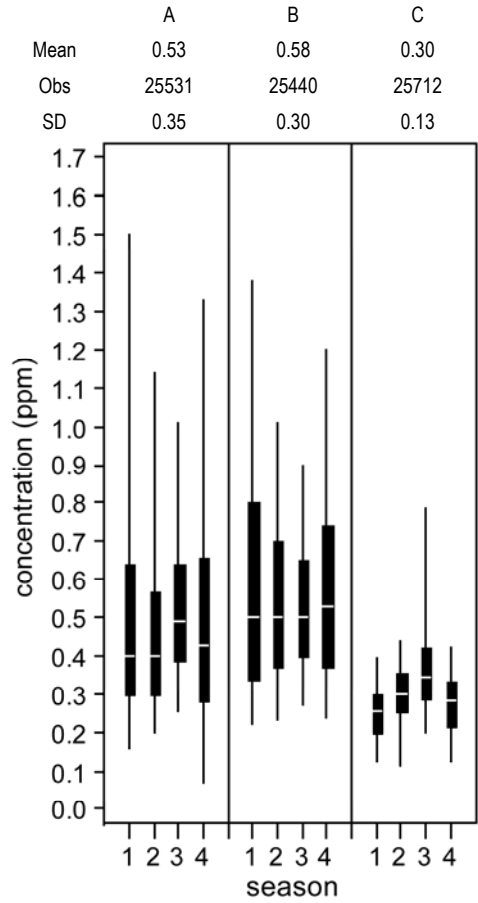
Boston Combined Statistical Area

Figure A-29.   Map of CO monitor locations with AQS Site IDs for Boston, MA.

Table A-3. 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.

Boston

	A	B	C	D	E	F	G
A	1.00	0.35	0.50	0.49	0.41	0.50	0.40
	0.0	0.4	0.4	0.5	0.4	0.6	0.4
	0.00	0.58	0.48	0.42	0.41	0.44	0.40
	0.0	37.2	39.7	57.9	41.3	18.3	89.1
B		1.00	0.52	0.34	0.27	0.35	0.34
		0.0	0.4	0.6	0.5	0.7	0.4
		0.00	0.56	0.59	0.58	0.60	0.55
		0.0	2.5	58.0	78.2	55.1	60.2
C			1.00	0.37	0.26	0.38	0.36
			0.0	0.5	0.5	0.6	0.4
			0.00	0.45	0.45	0.46	0.47
			0.0	58.9	80.7	57.5	58.7
D				1.00	0.40	0.46	0.34
				0.0	0.4	0.5	0.5
				0.00	0.28	0.25	0.39
				0.0	85.8	61.5	58.9
E					1.00	0.49	0.29
					0.0	0.5	0.4
					0.00	0.30	0.37
					0.0	26.1	128.6
F						1.00	0.43
						0.0	0.6
						0.00	0.39
						0.0	102.6
G							1.00
							0.0
							0.00
							0.0

Legend

r
P90
COD
d

	A	B	C	D	E	F	G
Mean	0.33	0.26	0.36	0.53	0.45	0.60	0.34
Obs	24362	24134	24260	24446	25197	25869	23707
SD	0.22	0.24	0.26	0.23	0.27	0.37	0.22

Figure A-30. **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.**
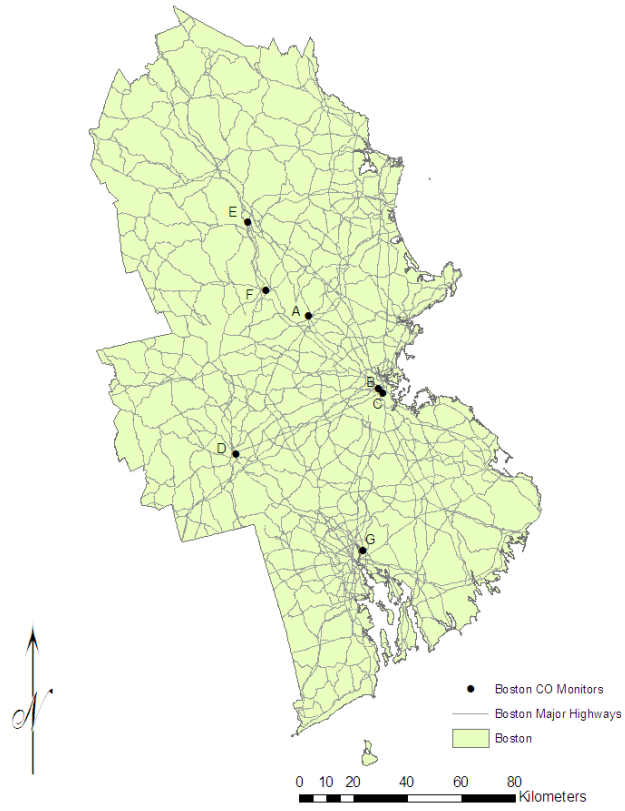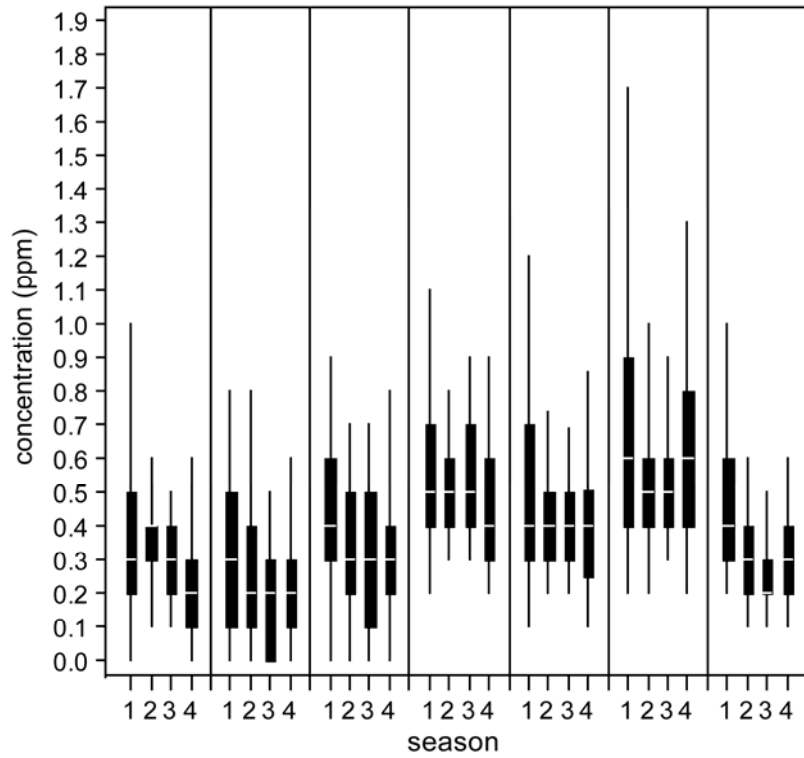
Denver Combined Statistical Area

Figure A-31.   Map of CO monitor locations with AQS Site IDs for Denver, CO.

Table A-4. 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 Denver, CO.

Denver

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

Legend
r
P90
COD
d

	A	B	C	D	E
Mean	0.52	0.42	0.65	0.52	0.55
Obs	25920	25559	25959	25552	26048
SD	0.36	0.38	0.42	0.46	0.46

Figure A-32.   Box plots illustrating the seasonal distribution of hourly CO concentrations in Denver, CO. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.
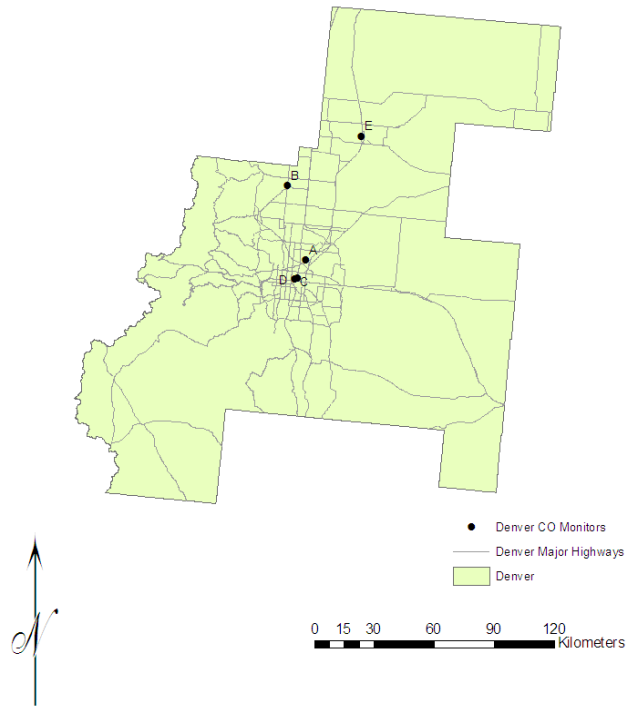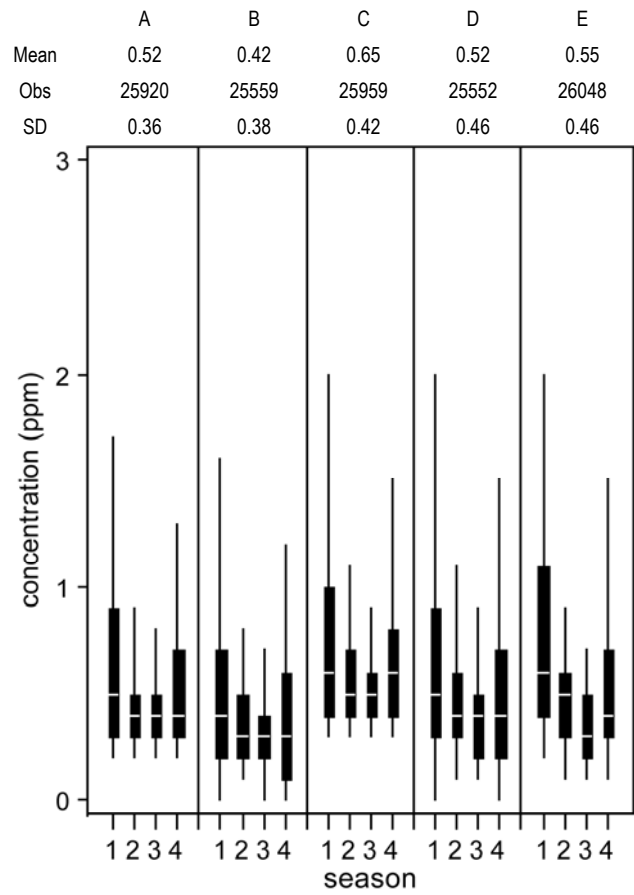
Houston Combined Statistical Area

Figure A-33.   Map of CO monitor locations with AQS Site IDs for Houston, TX.

Table A-5. 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.

Houston

	A	B	C	D	E
A	1.00	0.72	0.45	0.56	0.68
	0.0	0.3	0.4	0.5	0.3
	0.00	0.29	0.47	0.73	0.24
	0.0	17.5	16.7	19.8	32.2
B		1.00	0.56	0.65	0.63
		0.0	0.4	0.5	0.4
		0.00	0.47	0.73	0.29
		0.0	16.3	25.2	39.7
C			1.00	0.53	0.43
			0.0	0.5	0.4
			0.00	0.74	0.47
			0.0	9.3	23.5
D				1.00	0.57
				0.0	0.4
				0.00	0.72
				0.0	14.5
E					1.00
					0.0
					0.00
					0.0

Legend
r
P90
COD
d

	A	B	C	D	E
Mean	0.42	0.39	0.35	0.14	0.33
Obs	23997	25241	24922	25285	24480
SD	0.27	0.33	0.26	0.22	0.16

Figure A-34. **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.**
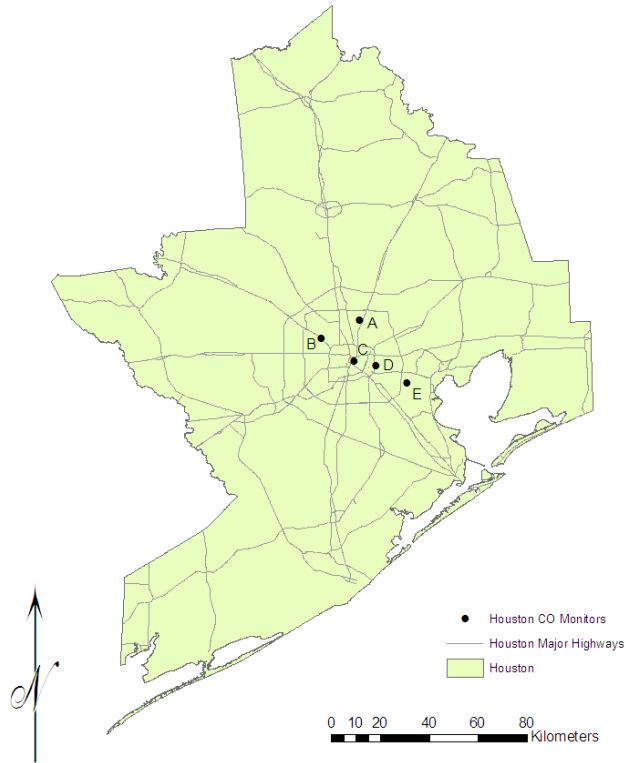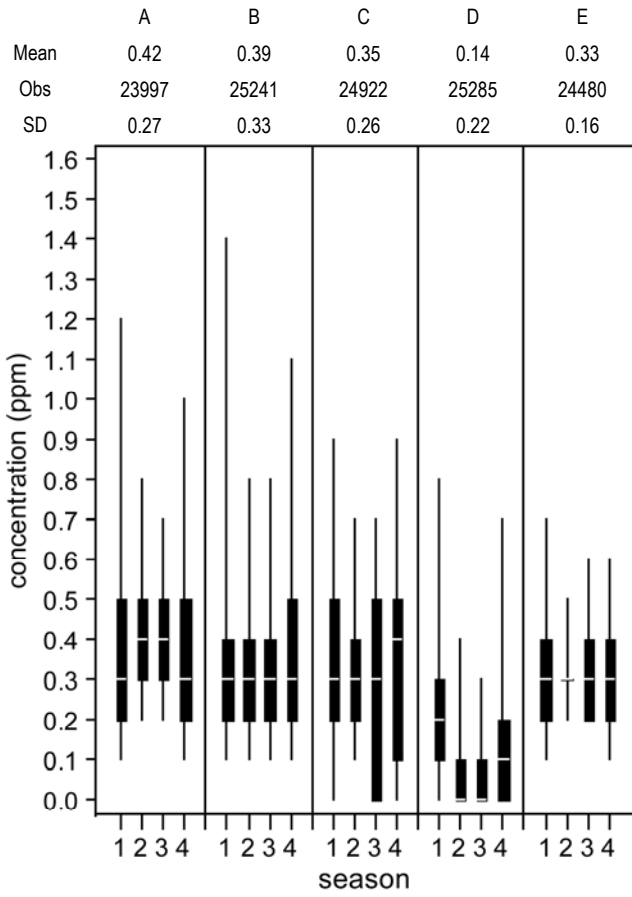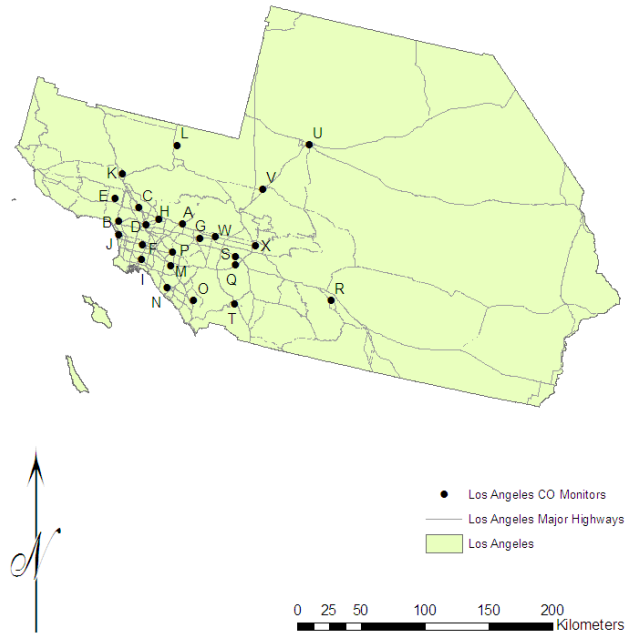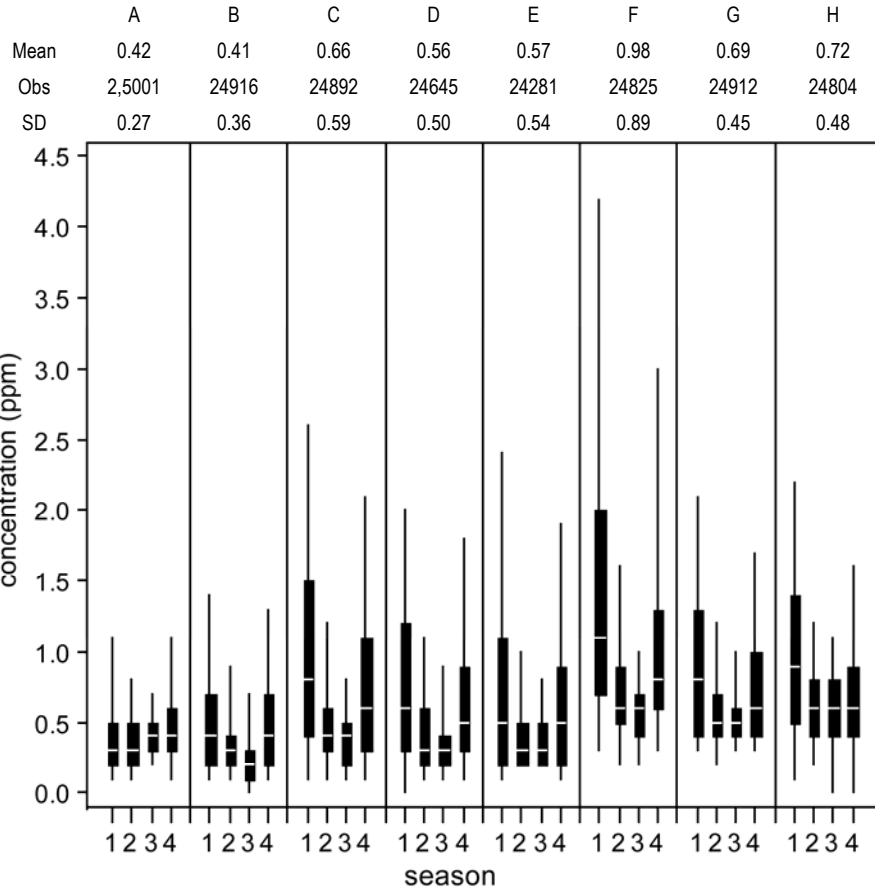
Figure A-35.   Map of CO monitor locations with AQS Site IDs for Los Angeles, CA.
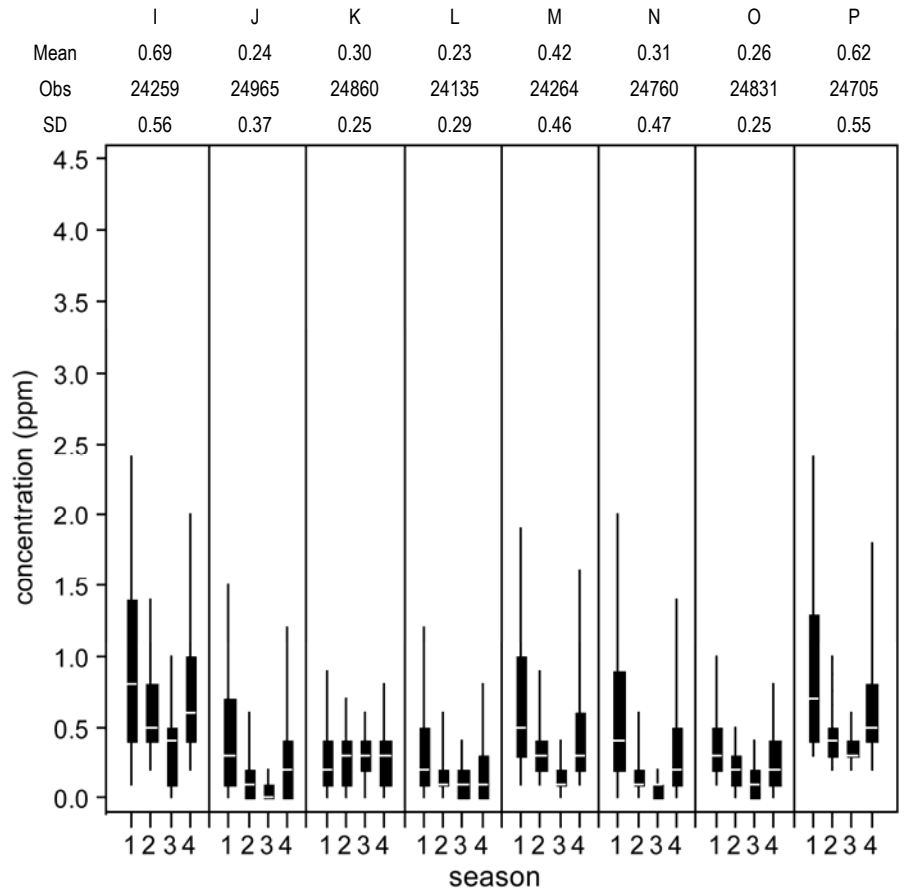
Table A-6. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Los Angeles, CA.

Los Angeles

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
A	1.00	0.45	0.43	0.46	0.44	0.21	0.57	0.41	0.17	0.19	0.43	0.27	0.29	0.14	0.42	0.34	0.54	0.33	0.47	0.56	0.17	0.24	0.61	0.48
	0.0	0.5	1.0	0.8	0.7	1.5	0.8	0.8	1.1	0.7	0.5	0.6	0.6	0.7	0.5	0.8	0.7	0.5	0.8	0.4	0.6	0.6	0.5	0.6
	0.00	0.38	0.35	0.38	0.33	0.44	0.33	0.43	0.47	0.72	0.47	0.62	0.43	0.64	0.52	0.33	0.33	0.36	0.43	0.38	0.62	0.50	0.30	0.35
	0	50.0	36.5	29.0	56.5	35.0	17.7	18.7	42.4	51.0	61.9	62.2	33.9	51.2	60.6	23.6	52.6	131.4	49.2	74.8	117.7	68.4	27.4	59.9
B		1.00	0.69	0.71	0.64	0.50	0.63	0.49	0.43	0.59	0.36	0.42	0.59	0.47	0.57	0.59	0.57	0.35	0.55	0.55	0.25	0.41	0.50	0.53
		0.0	0.8	0.6	0.7	1.3	0.7	0.8	0.9	0.6	0.6	0.7	0.5	0.7	0.6	0.6	0.7	0.6	0.7	0.5	0.7	0.6	0.6	0.6
		0.00	0.38	0.38	0.34	0.50	0.41	0.49	0.48	0.69	0.50	0.60	0.39	0.59	0.50	0.37	0.42	0.38	0.46	0.39	0.62	0.50	0.40	0.41
		0	18.9	21.2	17.8	26.4	65.0	31.6	35.2	11.4	37.4	74.9	53.7	64.4	85.9	48.5	98.1	178.1	96.1	112.0	161.1	115.3	76.4	109.1
C			1.00	0.84	0.74	0.70	0.78	0.67	0.62	0.64	0.39	0.59	0.72	0.70	0.69	0.75	0.70	0.40	0.52	0.58	0.35	0.58	0.59	0.65
			0.0	0.5	0.6	0.9	0.5	0.7	0.8	1.0	1.1	1.1	0.7	0.9	1.0	0.6	0.6	1.2	0.8	1.0	1.2	1.0	0.7	0.7
			0.00	0.29	0.28	0.35	0.26	0.39	0.41	0.72	0.52	0.65	0.41	0.63	0.56	0.26	0.29	0.46	0.42	0.46	0.67	0.53	0.29	0.35
			0	14.7	20.0	29.1	53.5	18.1	40.8	27.0	30.1	57.4	51.8	66.3	84.6	43.6	88.2	167.7	85.3	106.5	142.7	97.8	63.8	96.3
D				1.00	0.64	0.74	0.77	0.67	0.60	0.59	0.34	0.53	0.70	0.58	0.63	0.74	0.62	0.32	0.49	0.53	0.34	0.51	0.57	0.58
				0.0	0.7	1.0	0.5	0.7	0.8	0.8	0.9	0.9	0.6	0.8	0.8	0.5	0.6	1.0	0.8	0.8	1.0	0.8	0.6	0.6
				0.00	0.34	0.41	0.33	0.44	0.45	0.73	0.52	0.63	0.40	0.63	0.55	0.31	0.37	0.46	0.45	0.46	0.66	0.53	0.36	0.39
				0	31.8	15.3	43.8	11.7	27.1	22.7	44.7	67.5	37.3	51.6	70.2	29.8	77.4	157.4	75.1	93.4	143.4	95.9	55.2	87.9
E					1.00	0.49	0.70	0.54	0.44	0.52	0.53	0.53	0.61	0.57	0.55	0.61	0.73	0.42	0.62	0.66	0.31	0.55	0.58	0.71
					0.0	1.2	0.6	0.8	0.9	0.9	0.8	0.9	0.7	0.8	0.8	0.7	0.6	0.9	0.7	0.8	1.0	0.8	0.6	0.6
					0.00	0.41	0.30	0.42	0.44	0.72	0.49	0.62	0.41	0.62	0.54	0.29	0.29	0.40	0.40	0.40	0.64	0.50	0.30	0.32
					0	42.1	73.4	38.0	52.3	29.1	20.4	64.0	68.3	80.7	101.2	61.5	108.0	187.6	105.2	125.1	158.2	115.6	83.8	116.3
F						1.00	0.65	0.53	0.70	0.63	0.23	0.55	0.71	0.67	0.57	0.78	0.54	0.28	0.35	0.39	0.33	0.51	0.39	0.44
						0.0	1.0	1.0	1.0	1.5	1.6	1.6	1.1	1.3	1.5	0.9	1.1	1.7	1.2	1.6	1.7	1.5	1.3	1.3
						0.00	0.29	0.39	0.39	0.76	0.60	0.72	0.51	0.70	0.65	0.30	0.30	0.56	0.45	0.56	0.73	0.61	0.35	0.42
						0	45.0	23.8	11.8	20.4	58.2	82.5	27.4	38.6	59.5	23.8	74.8	154.5	73.7	86.0	152.6	103.4	57.0	88.6
G							1.00	0.65	0.52	0.51	0.47	0.61	0.69	0.60	0.70	0.77	0.78	0.47	0.60	0.69	0.40	0.58	0.78	0.68
							0.0	0.6	0.8	1.0	0.9	0.9	0.7	0.9	0.9	0.5	0.4	1.0	0.7	0.8	1.1	0.9	0.5	0.6
							0.00	0.34	0.38	0.73	0.53	0.66	0.44	0.66	0.58	0.20	0.19	0.47	0.38	0.46	0.68	0.54	0.18	0.31
							0	35.4	48.6	63.9	79.6	75.4	31.4	46.3	48.9	24.3	35.0	114.2	31.8	58.1	113.3	62.4	12.0	44.2
H								1.00	0.41	0.40	0.32	0.45	0.54	0.50	0.55	0.58	0.53	0.39	0.39	0.47	0.31	0.46	0.53	0.52
								0.0	0.9	1.0	1.0	1.0	0.8	0.9	0.9	0.7	0.7	1.0	0.8	0.9	1.1	0.9	0.7	0.7
								0.00	0.46	0.75	0.58	0.70	0.52	0.68	0.62	0.37	0.35	0.54	0.46	0.53	0.71	0.59	0.35	0.41
								0	34.7	34.4	46.2	59.6	37.7	54.0	69.5	28.1	70.1	149.6	67.2	89.2	131.7	84.3	46.0	78.6
I									1.00	0.59	0.15	0.43	0.63	0.64	0.48	0.62	0.46	0.24	0.31	0.36	0.24	0.43	0.28	0.39
									0.0	1.0	1.2	1.1	0.8	0.9	1.1	0.7	0.8	1.2	1.0	1.1	1.3	1.1	0.9	0.9
									0.00	0.75	0.60	0.69	0.48	0.64	0.58	0.37	0.39	0.53	0.48	0.54	0.70	0.59	0.41	0.46
									0	26.4	69.4	94.0	23.2	29.5	52.1	24.6	74.1	152.4	74.0	81.1	159.7	109.6	60.3	90.1
J										1.00	0.24	0.39	0.58	0.60	0.42	0.59	0.45	0.26	0.43	0.43	0.18	0.41	0.27	0.43
										0.0	0.6	0.6	0.6	0.5	0.5	0.8	0.9	0.5	0.9	0.5	0.6	0.6	0.9	0.8
										0.00	0.73	0.74	0.71	0.69	0.73	0.72	0.73	0.70	0.74	0.70	0.75	0.72	0.73	0.72
										0	48.7	84.4	47.4	55.8	78.3	44.2	95.0	174.8	93.7	106.1	166.0	118.6	75.8	108.0
K											1.00	0.40	0.29	0.25	0.28	0.34	0.54	0.40	0.46	0.56	0.25	0.39	0.53	0.50
											0.0	0.5	0.7	0.7	0.5	0.9	0.8	0.4	0.9	0.3	0.5	0.5	0.6	0.6
											0.00	0.62	0.53	0.67	0.59	0.52	0.53	0.45	0.56	0.47	0.62	0.54	0.51	0.51
											0	48.4	81.8	96.2	114.6	73.4	114.5	192.2	110.8	135.3	148.8	110.7	88.3	119.3
L												1.00	0.56	0.55	0.51	0.63	0.56	0.41	0.41	0.50	0.45	0.67	0.49	0.50
												0.0	0.7	0.6	0.4	0.9	0.9	0.4	0.9	0.4	0.4	0.4	0.7	0.7
												0.00	0.60	0.66	0.61	0.64	0.67	0.56	0.67	0.57	0.62	0.57	0.65	0.64
												0	94.7	112.0	122.7	84.2	104.6	171.9	99.2	132.5	104.0	75.4	77.9	100.4
M													1.00	0.75	0.67	0.81	0.62	0.37	0.49	0.53	0.31	0.54	0.47	0.55
													0.0	0.5	0.5	0.5	0.7	0.7	0.8	0.6	0.8	0.6	0.7	0.6
													0.00	0.55	0.46	0.38	0.46	0.41	0.49	0.42	0.62	0.50	0.45	0.46
													0	17.3	32.9	10.5	51.3	129.2	51.7	58.7	144.7	93.7	41.6	68.5

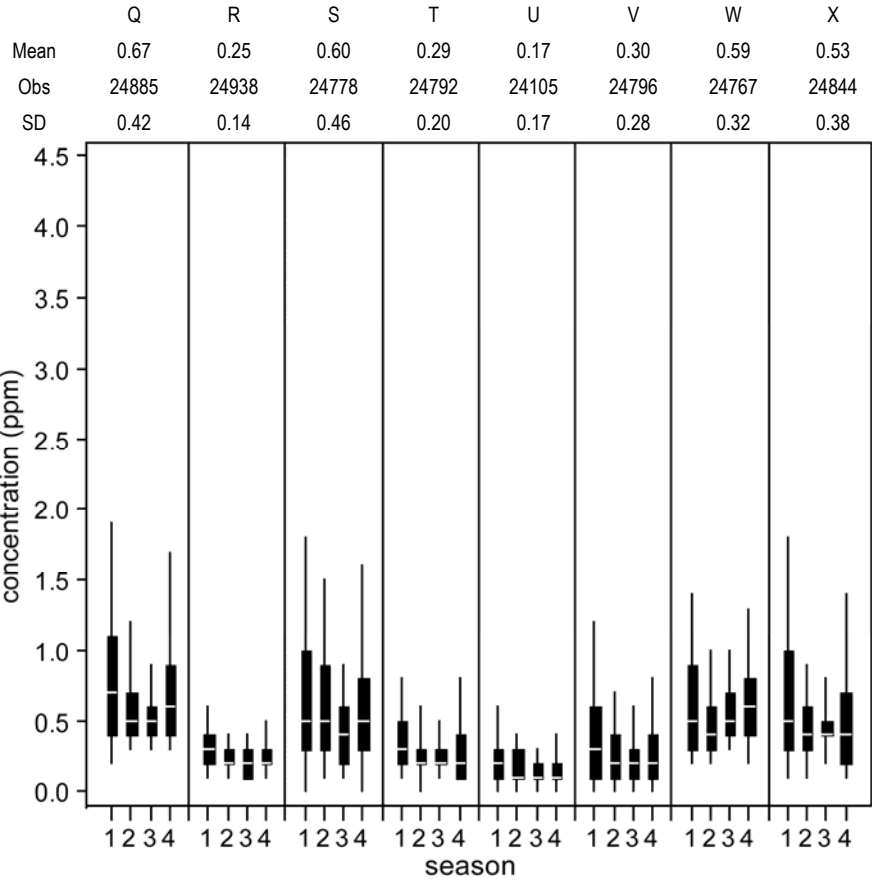|	N	O	P	Q	R	S	T	U	V	W	X
N	1.00	0.62	0.72	0.56	0.34	0.40	0.46	0.28	0.55	0.36	0.50
	0.0	0.5	0.7	0.8	0.6	0.9	0.5	0.7	0.6	0.8	0.7
	0.00	0.56	0.62	0.66	0.59	0.67	0.59	0.69	0.62	0.65	0.64
	0	23.7	27.9	57.1	129.6	59.3	55.1	158.5	107.5	54.9	76.9
O		1.00	0.67	0.61	0.44	0.43	0.51	0.33	0.45	0.57	0.51
		0.0	0.8	0.8	0.3	0.9	0.3	0.4	0.4	0.7	0.6
		0.00	0.54	0.58	0.47	0.59	0.50	0.63	0.56	0.56	0.56
		0	41.5	43.3	107.9	47.5	32.4	152.3	102.5	52.6	64.6
P			1.00	0.66	0.40	0.50	0.55	0.34	0.58	0.54	0.55
			0.0	0.6	1.0	0.8	0.8	1.0	0.8	0.6	0.7
			0.00	0.24	0.42	0.38	0.43	0.66	0.51	0.25	0.33
			0	51.0	130.6	50.2	63.7	137.1	86.4	35.8	65.7
Q				1.00	0.48	0.67	0.72	0.35	0.55	0.70	0.73
				0.0	0.9	0.6	0.7	1.0	0.8	0.5	0.5
				0.00	0.47	0.37	0.46	0.68	0.54	0.20	0.30
				0	80.1	6.1	30.5	110.6	62.8	27.4	21.3
R					1.00	0.40	0.49	0.29	0.38	0.47	0.46
					0.0	0.9	0.3	0.3	0.4	0.7	0.7
					0.00	0.50	0.32	0.55	0.44	0.43	0.43
					0	82.4	75.7	123.6	102.8	104.2	73.3
S						1.00	0.66	0.19	0.38	0.54	0.64
						0.0	0.8	1.1	0.9	0.6	0.6
						0.00	0.49	0.69	0.58	0.37	0.41
						0	36.64	105.4	57.05	22.78	17.67
T							1.00	0.30	0.49	0.68	0.69
							0.0	0.4	0.4	0.6	0.6
							0.00	0.58	0.47	0.43	0.42
							0	137.8	92.3	54.8	48.0
U								1.00	0.43	0.36	0.31
								0.0	0.4	0.8	0.8
								0.00	0.59	0.66	0.65
								0	51.0	103.7	90.2
V									1.00	0.47	0.51
									0.0	0.7	0.6
									0.00	0.52	0.52
									0	52.7	44.9
W										1.00	0.64
										0.0	0.5
										0.00	0.29
										0	32.7
X											1.00
											0.0
											0.00
											0

Legend

r
P90
COD
d

Figure A-36a. Box plots illustrating the seasonal distribution of hourly CO concentrations in Los Angeles, CA. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.

|	I	J	K	L	M	N	O	P
Mean	0.69	0.24	0.30	0.23	0.42	0.31	0.26	0.62
Obs	24259	24965	24860	24135	24264	24760	24831	24705
SD	0.56	0.37	0.25	0.29	0.46	0.47	0.25	0.55

Figure A-36b. Box plots illustrating the seasonal distribution of hourly CO concentrations in Los Angeles, CA. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.

	Q	R	S	T	U	V	W	X
Mean	0.67	0.25	0.60	0.29	0.17	0.30	0.59	0.53
Obs	24885	24938	24778	24792	24105	24796	24767	24844
SD	0.42	0.14	0.46	0.20	0.17	0.28	0.32	0.38

Figure A-36c. Box plots illustrating the seasonal distribution of hourly CO concentrations in Los Angeles, CA. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.
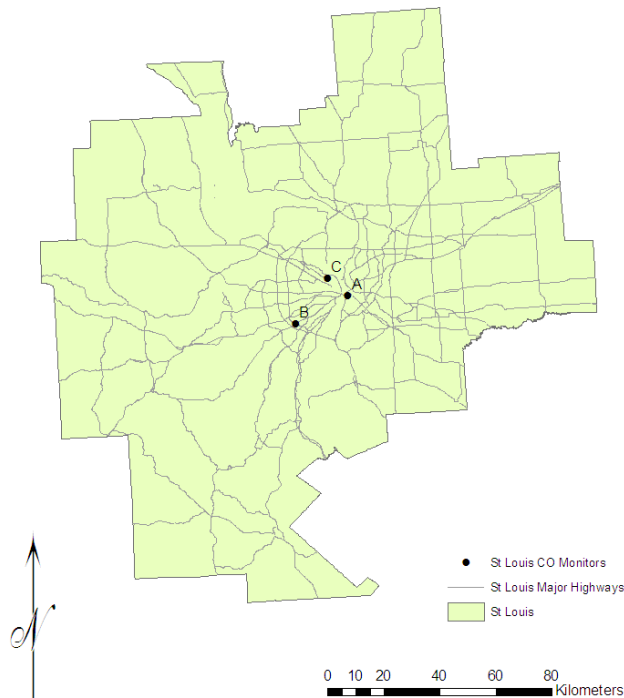
New York Combined Statistical Area
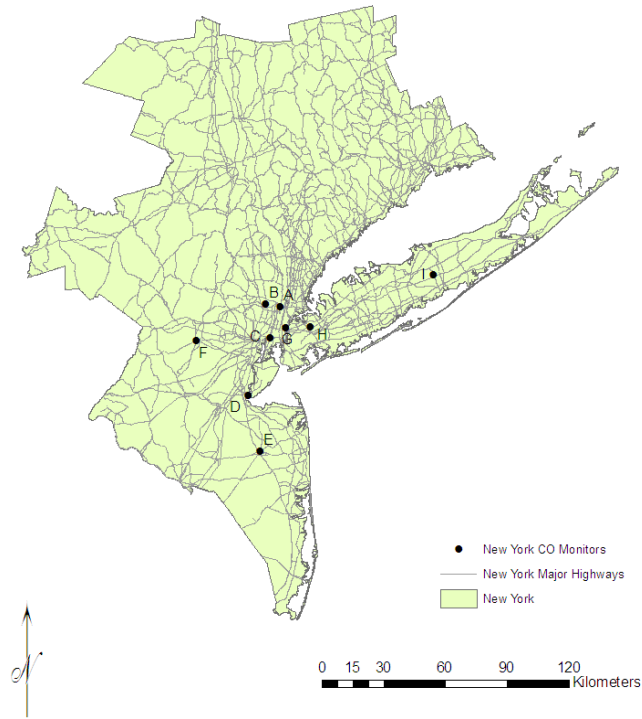
Figure A-37.   Map of CO monitor locations with AQS Site IDs for New York City, NY.

Table A-7. 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.

New York

	A	B	C	D	E	F	G	H	I
A	1.00	0.58	0.65	0.55	0.40	0.56	0.56	0.41	0.30
	0.0	0.4	0.7	0.4	0.4	0.4	0.4	0.5	0.8
	0.00	0.22	0.28	0.25	0.25	0.24	0.23	0.28	0.75
	0.0	7.0	15.9	45.8	70.6	43.7	10.5	17.8	76.5
B		1.00	0.64	0.55	0.35	0.54	0.54	0.59	0.49
		0.0	0.8	0.4	0.5	0.4	0.4	0.4	0.7
		0.00	0.29	0.23	0.26	0.23	0.23	0.23	0.74
		0.0	16.8	45.4	71.5	38.1	15.0	24.5	82.9
C			1.00	0.54	0.32	0.48	0.52	0.43	0.31
			0.0	0.9	0.9	0.9	0.7	0.9	1.3
			0.00	0.35	0.34	0.34	0.24	0.35	0.81
			0.0	29.9	55.0	35.7	8.9	20.5	85.5
D				1.00	0.50	0.57	0.41	0.46	0.33
				0.0	0.4	0.4	0.4	0.4	0.7
				0.00	0.24	0.23	0.28	0.27	0.72
				0.0	27.5	36.7	37.5	45.1	107.8
E					1.00	0.47	0.33	0.33	0.32
					0.0	0.4	0.4	0.4	0.6
					0.00	0.23	0.25	0.27	0.73
					0.0	61.9	61.0	65.0	120.3
F						1.00	0.41	0.34	0.31
						0.0	0.4	0.4	0.7
						0.00	0.26	0.27	0.72
						0.0	43.6	55.8	119.7
G							1.00	0.46	0.29
							0.0	0.4	0.7
							0.00	0.26	0.77
							0.0	12.3	76.8
H								1.00	0.43
								0.0	0.6
								0.00	0.73
								0.0	65.1
I									1.00
									0.0
									0.00
									0.0

Legend

r	
P90	
COD	
d	

	A	B	C	D	E	F	G	H	I
Mean	0.55	0.52	0.85	0.48	0.50	0.49	0.62	0.47	0.12
Obs	23113	25150	25646	25028	25727	25691	25547	25022	25749
SD	0.27	0.30	0.43	0.27	0.24	0.25	0.21	0.23	0.17
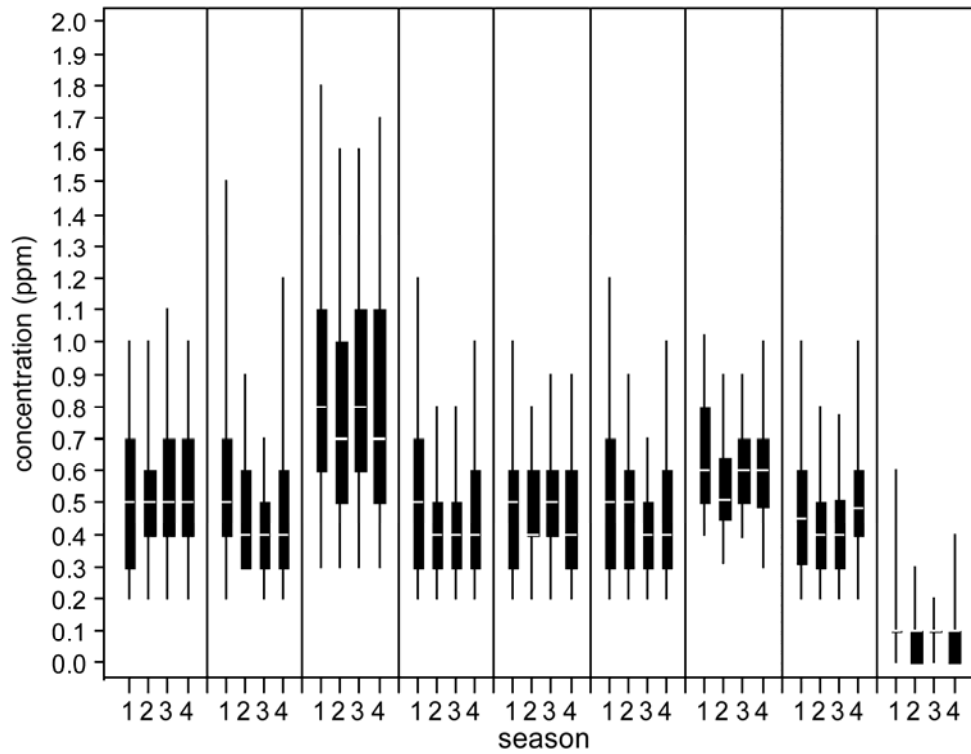
Figure A-38. **Box plots illustrating the seasonal distribution of hourly CO concentrations in New York City, NY. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.**
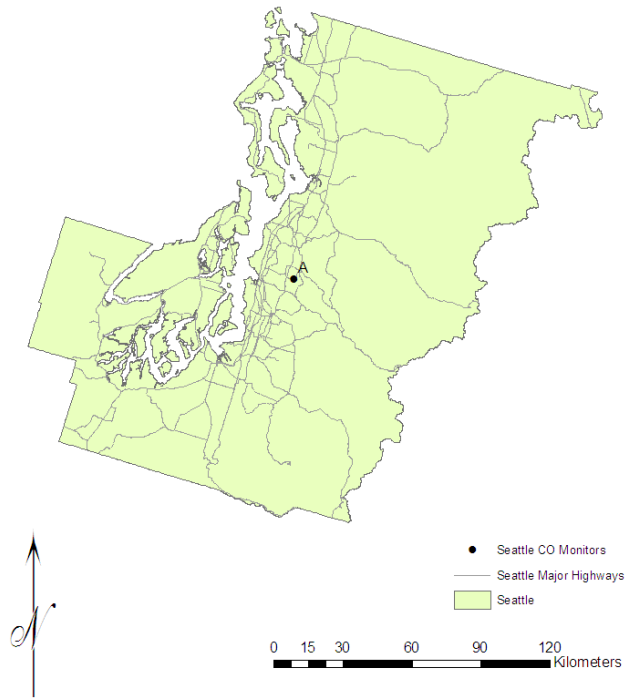
Figure A-39. **Map of CO monitor locations with AQS Site IDs for Seattle, WA.**

	A
Mean	0.75
Obs	25818
SD	0.49
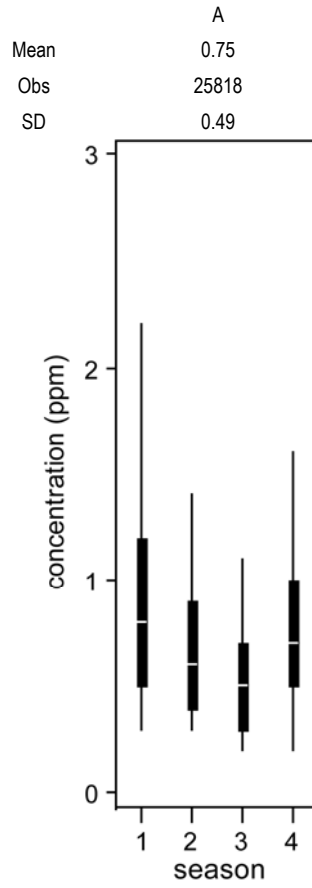
Figure A-40. Box plots illustrating the seasonal distribution of hourly CO concentrations in Seattle, WA. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.

St Louis Combined Statistical Area

Figure A-41. **Map of CO monitor locaitons with AQS Site IDs for St. Louis, MO.**

Table A-8. **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.**

St. Louis

	A	B	C
A	1.00	0.19	0.60
	0.0	0.5	0.3
	0.00	0.40	0.24
	0.0	21.2	9.5
B		1.00	0.19
		0.0	0.5
		0.00	0.42
		0.0	19.8
C			1.00
			0.0
			0.00
			0.0

Legend
r
P90
COD
d
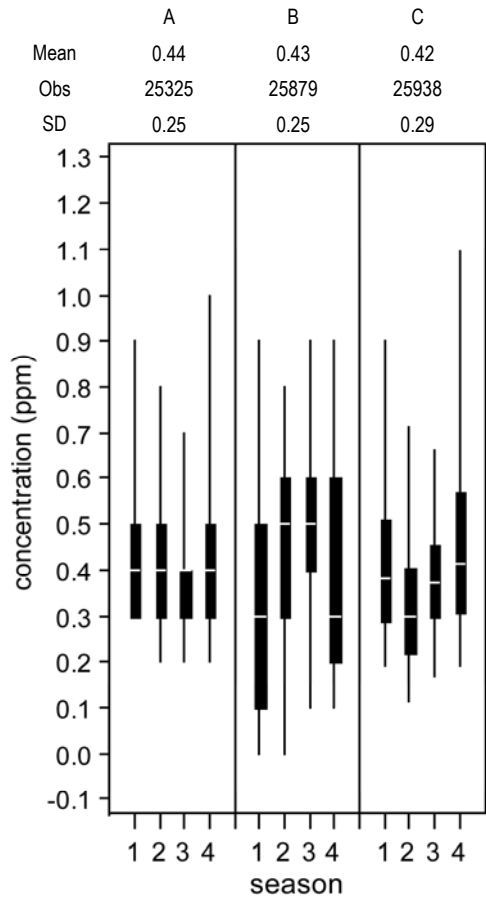
Figure A-42. Box plots illustrating the seasonal distribution of hourly CO concentrations in St. Louis, MO. Note: 1 = winter, 2, = spring, 3 = summer, and 4 = fall on the x-axis.
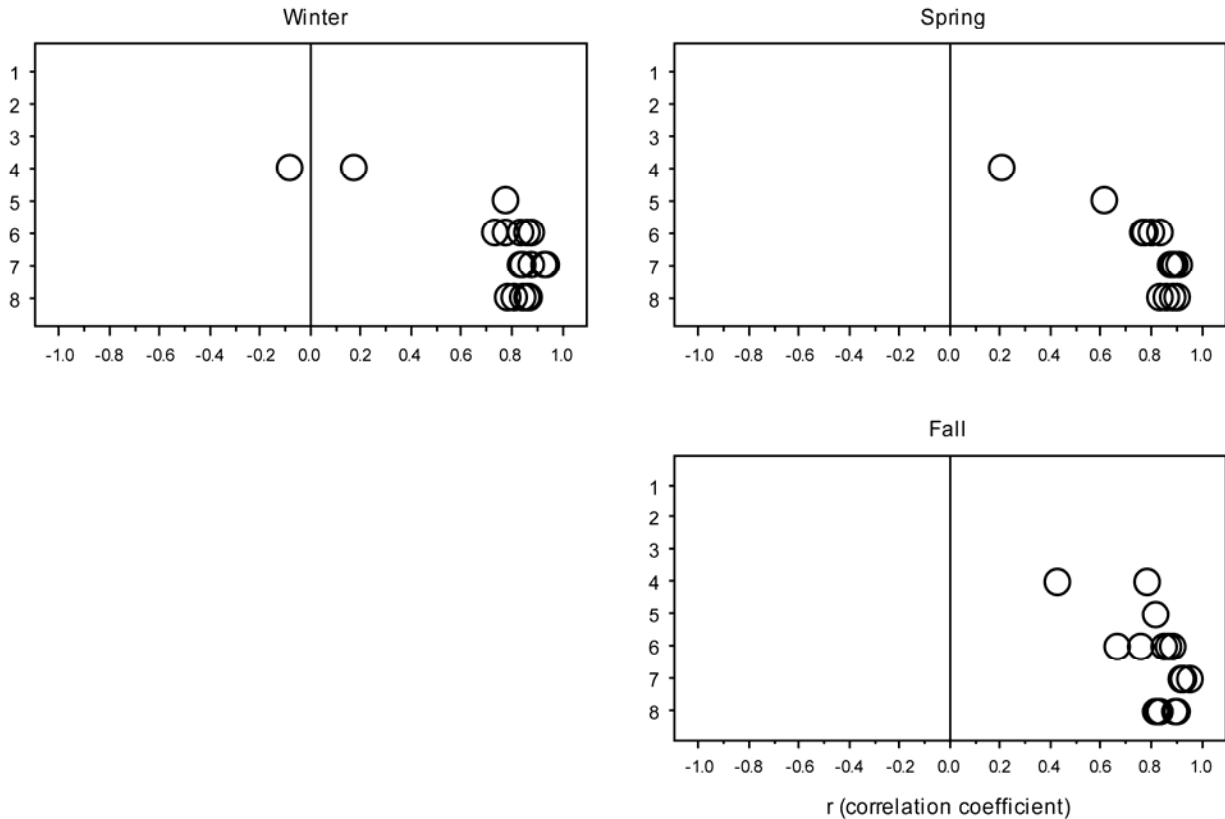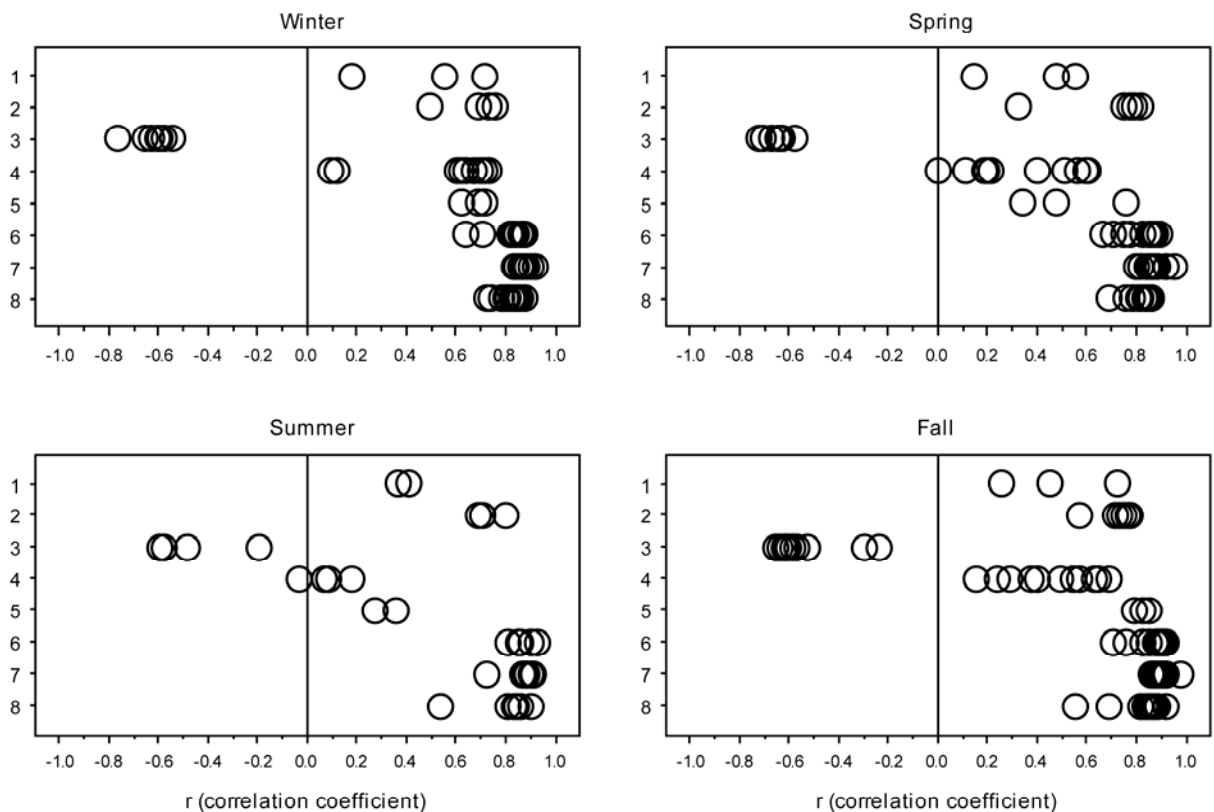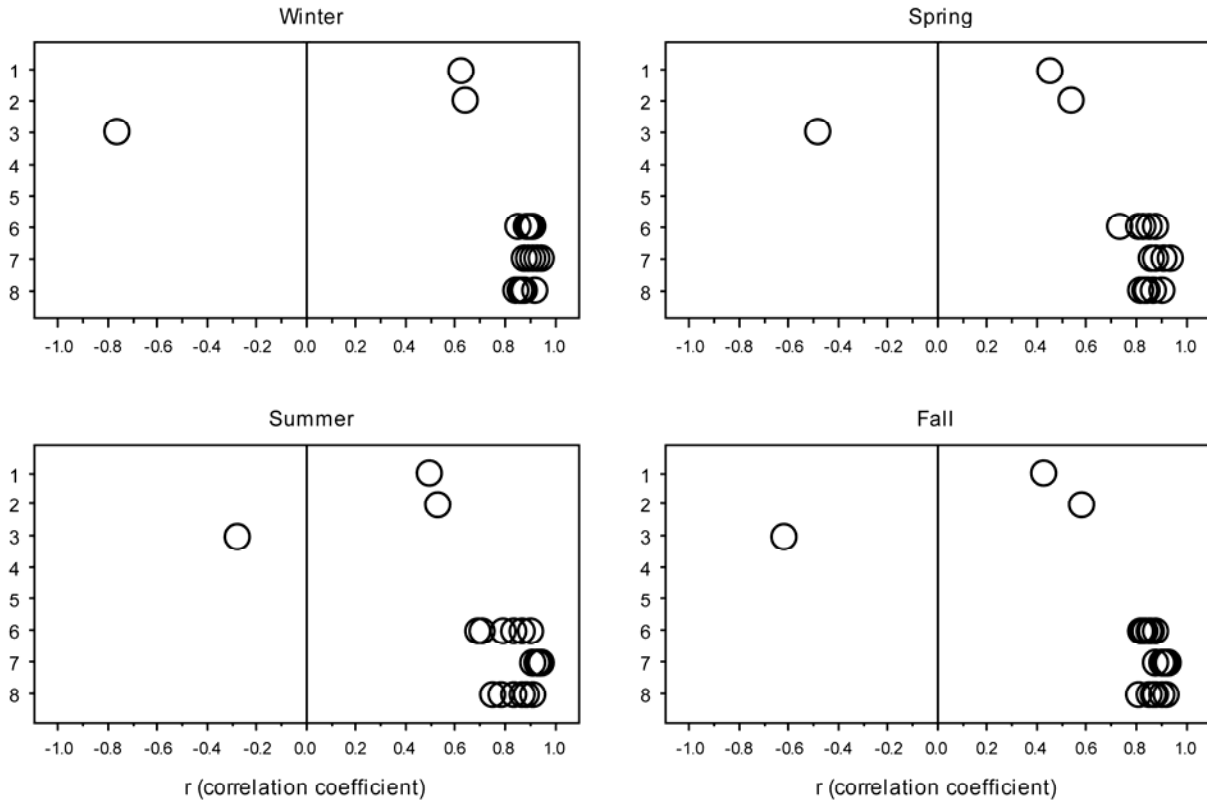
Figure A-43. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Anchorage, AK. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations 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.
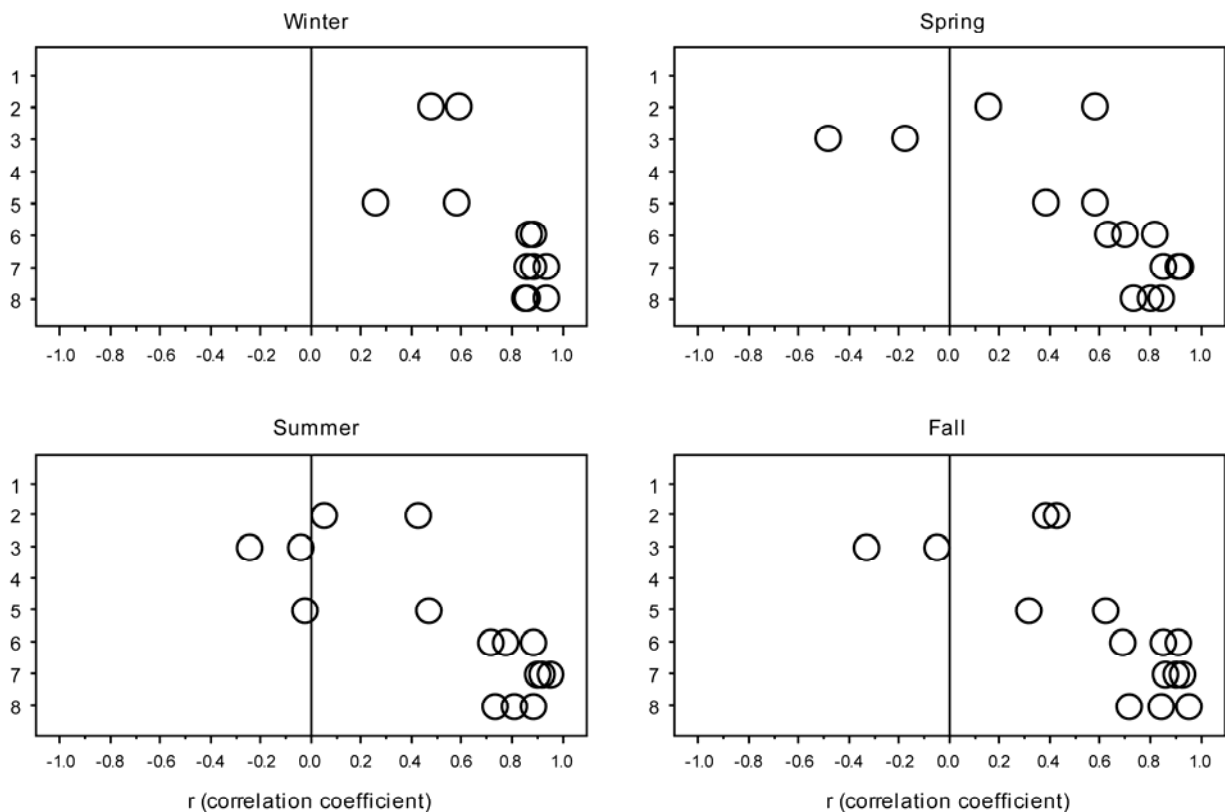
Figure A-44. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Atlanta, GA. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations 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.)
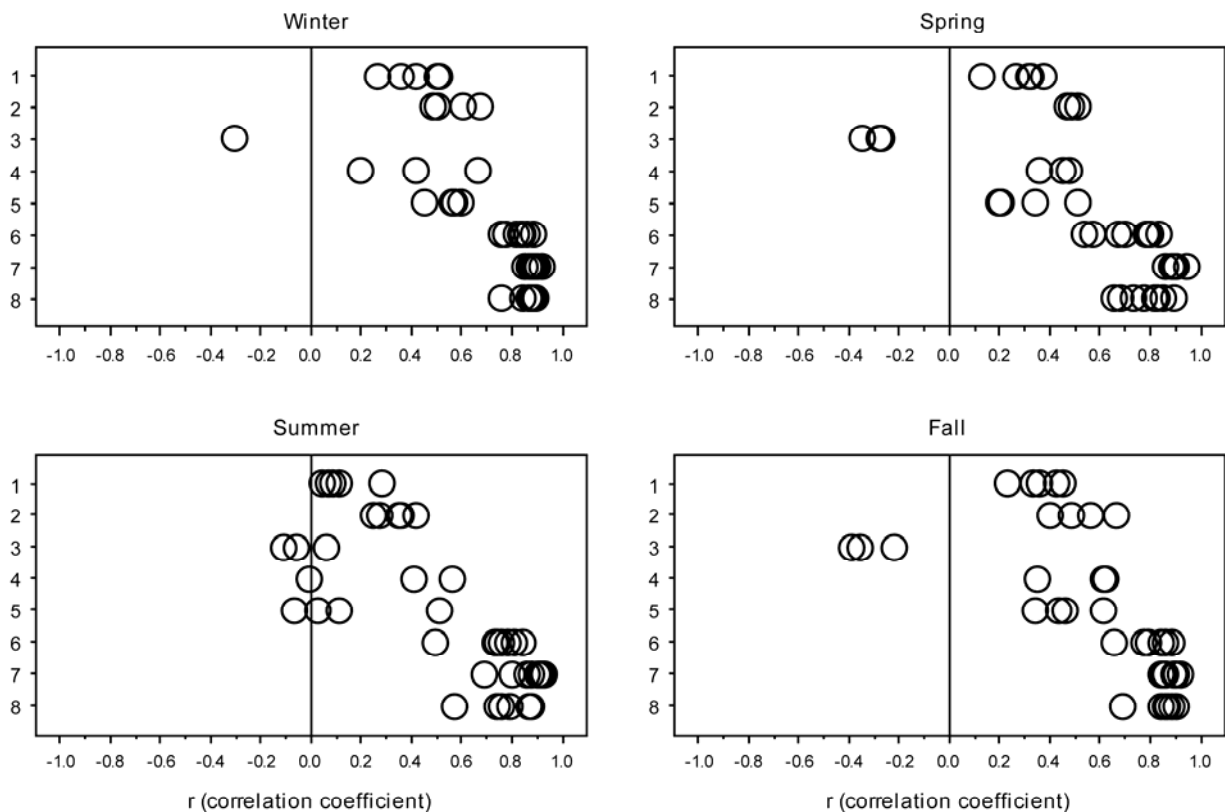
Figure A-45. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Boston, MA. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations 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.) Red bars denote the median, and green stars denote the arithmetic mean.
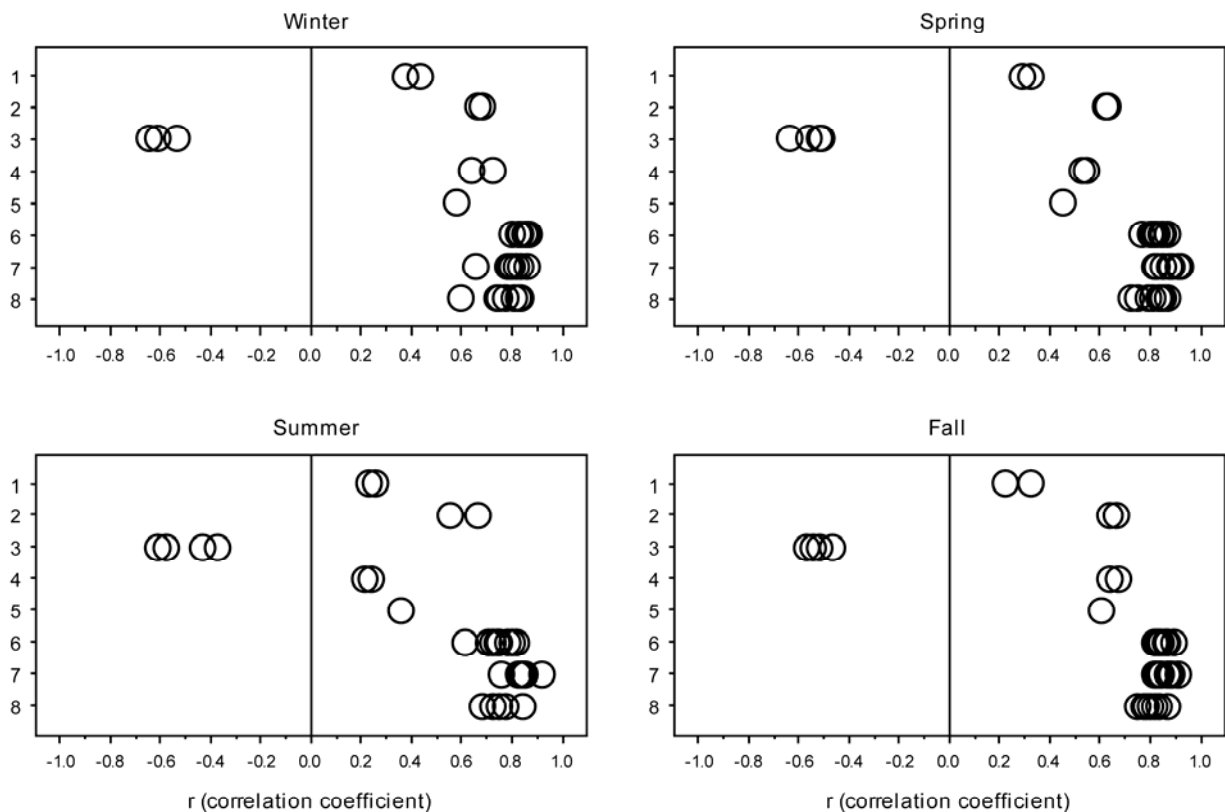
Figure A-46. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Denver, CO. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations 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.) Red bars denote the median, and green stars denote the arithmetic mean.
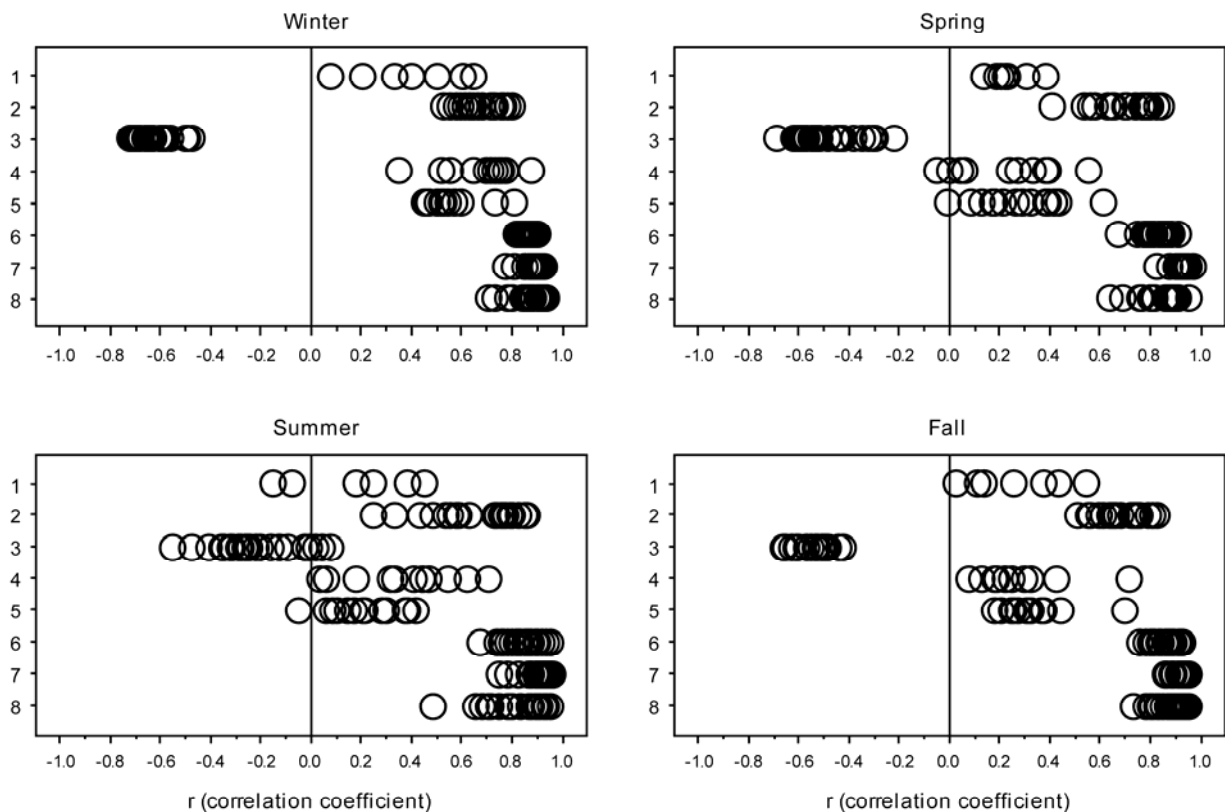
Figure A-47. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Los Angeles, CA. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations 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.)
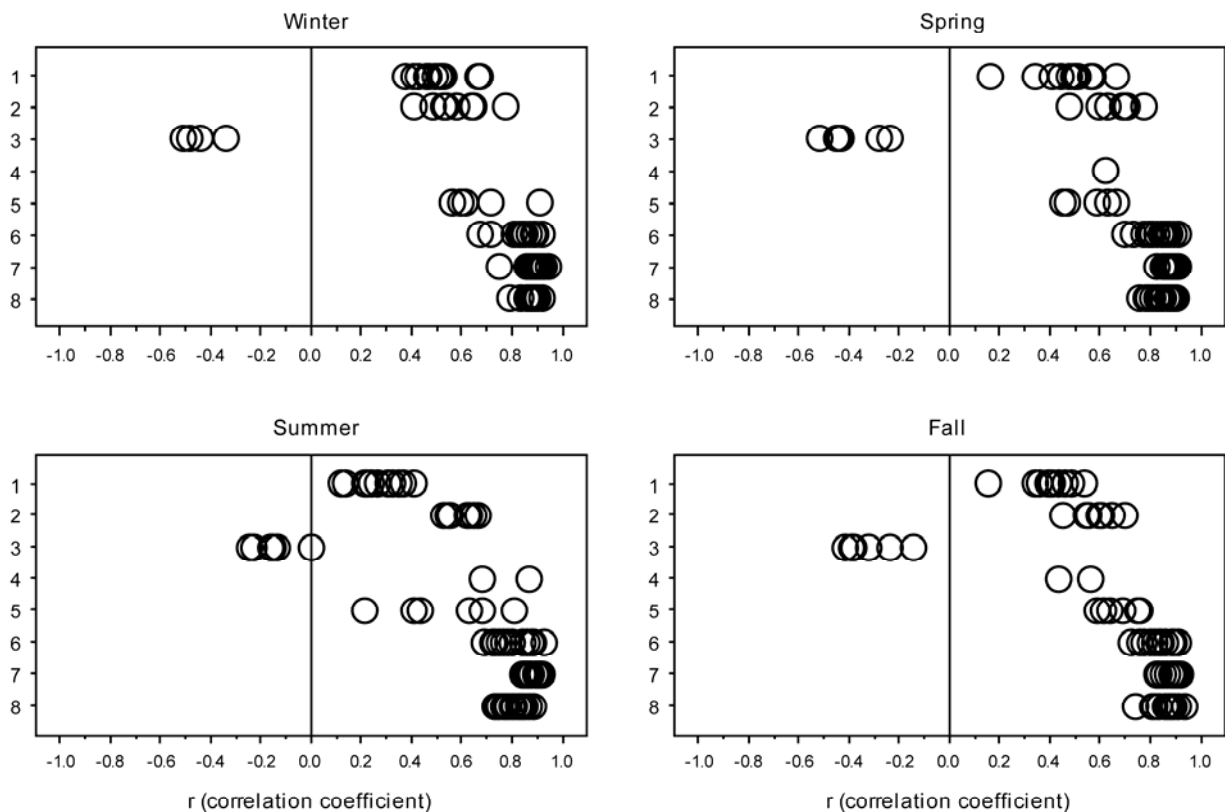
Figure A-48. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for New York City, NY. Also shown are correlations between 24-h average CO concentration with (6) daily max 1-h and (7) daily max 8-h CO 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 Phoenix, AZ. Also shown are correlations between 24-h average 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. 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 average 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.)

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Annex B. Dosimetry Studies

Table B-1. Recent studies related to CO dosimetry and pharmacokinetics.

Reference	Purpose	Findings
Alcantara et al. (2007)	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)	To determine if low concentrations of CO would affect exercise performance and myocardial perfusion in young healthy men.	Men with COHb levels between 4-6% 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.
Andersson et al. (2000)	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.
Bruce and Bruce (2003)	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)	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 non-muscle 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 et al. (2008)	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 intra-tissue pathways and diffusion of blood gases into tissues from pre-capillary vessels like arterioles.	The former model of Bruce and Bruce (2006) 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 non-muscle tissue. CO uptake from blood by muscle is much slower than O_2, thus COHb% will fall rapidly while COMb% could remain high.
Carraway et al. (2000)	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)	To describe a new method for measurement of CO diffusing capacity (D_LCO) and alveolar volume (V_A) in sleeping infants (6-22 months old), using a single 4-sec 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)	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 P_{CO} under normoxic and hyperoxic conditions, but diffusion rate limited under hypoxic and high P_{CO} conditions.
Cronje et al. (2004)	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] dissociate during CO inhalation, but [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.

Reference	Purpose	Findings
Dutton et al. (2001)	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 average 0.36 ppm over 4 hours. PAH 4-h time average reached 35 ng/m^3.
Hampson (2007)	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%.
Hsia (2002)	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, cardiac output, etc.
Lamberto et al. (2004)	To evaluate which component, alveolar membrane diffusing capacity (D_m) and pulmonary capillary blood volume (V_c), 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. D_m accounted for the majority of the decrease in D_LCO and was predictive for gas exchange abnormalities.
Levesque et al. (2000)	To describe the results of air quality monitoring in an indoor ice skating rink during Monster Truck and car demolition exhibitions.	Maximum time-weighted average levels of CO were 100 ppm with several peaks exceeding 200 ppm (maximum: 1,600 ppm).
Marks et al. (2002)	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.
Merx et al. (2001)	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.
Pelham et al. (2002)	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.
Pesola et al. (2004)	To determine if healthy African Americans may be misdiagnosed has 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)	To determine if healthy Asians may be misdiagnosed has 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.
Prommer and Schmidt (2007)	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). 2.3% increase in total Hb mass would be found if CO diffusion was not included.
Richardson et al. (2002)	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, CO_{norm}, and CO_{hyper}. 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.
Shimazu et al. (2000)	To study the effects of short-term (minutes) or long-term (several hours) 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)	To discuss the findings of Weaver et al. (2000) on COHb $t_{1/2}$.	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) paper.
Takeuchi et al. (2000)	To examine the relationship between minute ventilation and rate of COHb reduction during breathing 100% O_2 and during normocapnic hyperoxic hyperpnea.	Patients were exposed to 400 to 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.
Vreman et al. (2005)	To develop a sensitive and reproducible method of CO quantification in rodent (mouse and rat) tissue pre- and post-exposure 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).

Reference	Purpose	Findings
Vreman et al. (2006)	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.
Weaver et al. (2000)	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 $t_{1/2}$ 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.
Wu and Wang (2005)	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. Also, it discusses the potential pharmacological and therapeutic applications for CO.

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) **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 years **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: Dales et al. (2004) **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 years (mean 65 years) **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)
Author: Gold et al. (2000) **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 years **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) **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 years **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: Holguin et al. (2003) **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 years (mean age 79 years) **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: Liao et al. (2004) **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 years (mean 62 years) **Sample Description:** 6784 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 *$p < 0.05$
Author: Park et al. (2005b) **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 years **Sample Description:** 497 men from the Normative aging study in Greater Boston	**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. (1999a) **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 years **Sample Description:** 2681 men & 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 Respectively **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) **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 years (mean 55 years) **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 minutes) : 5, 10 Lag 5 minutes : 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) **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 years **Sample Description:** 28 subjects living at or near an apartment complex located on the same street at 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 to 10.5) 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) **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:** Age 55 – 68 years **Sample Description:** 6 male patients with angiographically verified CAD	**Averaging Time:** 24-h **Mean (SD) unit:** 4.6 ppm (maximum of CO episode) (personal monitoring) **Range (Min, Max):** 0.5, 27.4 (maximum of CO episode) **Copollutant:** NR	**Increment:** NR **RR Estimate [Lower CI, Upper CI]** Lags examined : 5 minute prior to CO episode, 5 minute 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) **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 years. **Sample Description:** 131 subjects with Stable CAD followed for 6 months with bi-weekly 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) **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 years – IQR 55- 73 years. **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.

ONSET OF CARDIAC ARRHYTHMIA

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Berger et al. (2006) **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 years (mean 76years) **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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Dockery et al. (2005) **Period of Study:** 1995 - 2002 **Location:** Boston, MA	**Health Outcome:** Tachyarrhythmias: **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** 19 – 90 years; mean age 64 years **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 2day 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) **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 years **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 **OR 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)
Author: Peters et al. (2000b) **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 age of 62 years **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. (Rich et al.) **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 years **Sample Description:** 34 patients who experienced at least 1 ICD discharge (8201 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) **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 & 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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Rich et al. (2006b) **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 : 0-23 h-ma 0-23h-ma : 0.99 (0.80-1.21)
Author: Rich et al. (2006a) **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 & 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: Sarnat et al. (2006) **Period of Study:** 24 weeks 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 years (mean age 71) **Sample Description:** 32 non-smoking 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) **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 (mean age 53) **Sample Description:** 50 patients who experienced 1 or more arrhythmia event days during the four years	**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)

CARDIAC ARREST

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Levy et al. (2001) **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 years **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) **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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)

MYOCARDIAL INFARCTION

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Peters et al. (2001) **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) **Period of Study:** 1992 - 1994 **Location:** Stockholm, Sweden	**Health Outcome:** MI **Study Design:** Case-control **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 45 – 70 years **Sample Description:** 1,397 cases, 1,870 controls	**Averaging Time:** **Mean (SD) unit:** 66.8 µg/m^3 (est. 30yr 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) Non-fatal 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)

CHANGES IN BLOOD PRESSURE

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ibalde-Mulli et al. (2001) **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 years **Sample Description:** 2,607 men & women aged 25-64 years	**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. (2004a) **Period of Study:** 1999 - 2001 **Location:** Boston, MA	**Health Outcome:** BP **Study Design:** Cohort/Panel **Statistical Analyses:** Random effects **Age Groups Analyzed:** 39 – 90 years **Sample Description:** 62 subjects with 631 total visits	**Averaging Time:** 1-h & 120-h avg **Mean (SD) unit:** Same Hr: 0.81 ppm 120 Hr av: 0.66 ppm **Range (Min, Max):** Same h: 10th = 0.48; 90th = 1.22 120-h av: 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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Baccarelli et al. (2007) **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 years (mean 43years) **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, free protein S for all lag periods.
Author: Liao et al. (2005) **Period of Study:** 1996 to 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 years **Sample Description:** 10208 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 10^3/mm^3) : 0.003 (0.017) Albumin (g/dL) : -0.018 (0.003)** ** p < 0.01

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Pekkanen et al. (2000) **Period of Study:** 1991 - 1993 **Location:** London, England	**Health Outcome:** Fibrinogen **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 35 – 55 years **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)
Author: Ruckerl et al. (2006) **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 years (mean age 66 years) **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) **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 years **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)
Author: Steinvil et al. (2008) **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 age 46 years **Sample Description:** 3659 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 week 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 week 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.

Table C-2.   Studies of CO exposure and cardiovascular hospital admissions and ED visits.

Study	Design	Concentrations	CO Effect Estimates (95% CI)

STROKE

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Chan et al. (2006) **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) **Period of Study:** 1994 - 2004 **Location:** Dijon, France	**Health Outcome (ICD9 or ICD10):** Stroke (Ischemic & Hemorrhagic) **Study Design:** Bi-directional Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** ≥ 40 **Sample Description:** NR	**Averaging Time:** 24-h **Mean (SD) unit:** 683 μg/m³ **Range (Min, Max):** 0, 4014 **Copollutant:** NR	**Increment:** 10 μg/m³ **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.
Author: Maheswaran et al. (2005b) **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 years **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. (2003b) **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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Villeneuve et al. (2006a) **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+ **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. (2005a) **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 years **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)

ISCHEMIC HEART DISEASE

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: D'Ippoliti et al. (2003) **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+ **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) **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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lanki et al. (2006) **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+ years **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)
Author: Lee et al. (2003b) **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 + **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 year: 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. (2005b) **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+ years **Sample Description:** 11,407 Emergency Hospital Admissions for CHD in patients 45+ years (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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Mann et al. (2002) **Period of Study:** 1988 - 1995 **Location:** Southern California	**Health Outcome (ICD9):** IHD (IHD) (410-414); Myocardial Infarction (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) **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:** 4979 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
Author: von Klot et al. (2005) **Period of Study:** 1992 - 2001 **Location:** 5 European cities: Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	**Health Outcome:** Hospital Cardiac (Myocardial Infacrtion (MI), Angina, Dysrythmia, Heart Failure) Re-admissions **Study Design:** Prospective Cohort **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** All **Sample Description:** 22006 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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lee et al. (2007a) **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:** 13475 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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Symons et al. (2006) **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. (2005b) **Period of Study:** 1987 - 1999 **Location:** Pennsylvania, PA	**Hospital Admissions** **Health Outcome (ICD9):** CHF (428, 428.1) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 65+ **Sample Description:** 54019 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)

CARDIOVASCULAR DISEASES – NON-SPECIFIC

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ballester et al. (2001) **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) **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) **Period of Study:** 1998 – 2001 **Location:** Brisbane, Canberra, Melbourne, Perth, Sydney Australia Auckland & Christchurch, New Zealand	**Hospital Admissions with Cardiovascular Diseases** **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 years & ≥ 65 years **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 years** 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 years** 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: Chang et al. (2005) **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: Fung et al. (2005) **Period of Study:** 1995 - 2000 **Location:** Windsor, Ontario, Canada	**Hospital Admissions of Cardiovascular Diseases** **Health Outcome (ICD9):** CHF (428); IHD (410 – 414); Dysrhythmias (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 years** 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 years** 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)
Author: Jalaludin et al. (2006) **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+ years **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 Cardiovascular Disease:** 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) **Period of Study:** 1993 - 1997 **Location:** Denver, CO	**Hospital Admissions for Cardiovascular Disease** **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 years **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.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Linn et al. (2000) **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 years **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) **Myocardial Infarction** 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
Author: Metzger et al. (2004a) **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) **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) **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.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Yang et al. (2004a) **Period of Study:** 1997 - 2000 **Location:** Kaohsiung City, Taiwan	**Health Outcome (ICD9:** Cardiovascular diseases (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) **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 weeks)	**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) **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:** 70249 live singleton births	**Averaging Time:** Land use regression 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) **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 weeks)	**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
Author: Conceicao et al. (2001) **Period of Study:** 1994 - 1997 **Location:** Sao Paulo, Brazil	**Health Outcome:** Child mortality, under 5 years 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 years of age [SE] ;** Lags examined : 0, 1, 2, 3 Lag 2 : 0.0306 (0.0076) (p < 0.01) Lag chosen for best fitting model

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Gilboa et al. (2005) **Period of Study:** 1997 - 2000 **Location:** Texas	**Health Outcome:** Birth defects (heart defects & 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 : weeks 3 – 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 & valve, atrial septal, pulmonary artery & valve, ventricular septal, endocardial cushion & mitral valve , cleft lip, cleft palate, aortic valve stenosis, coarctation of the aorta, ostium secundum.
Author: Gouveia et al. (2004) **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 weeks)	**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) **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 weeks)	**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) **Period of Study:** 1995 - 1999 **Location:** Seoul, South Korea	**Health Outcome:** Post-neonatal mortality (1 month – 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 month – 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)
Author: Huynh et al. (2006) **Period of Study:** 1999 - 2000 **Location:** California	**Health Outcome:** PTB (24-36 weeks gestation) **Study Design:** Case-control **Statistical Analyses:** Conditional Logistic regression **Age Groups Analyzed:** Cases = 24-36 weeks gestation; Controls = 39 – 44 weeks **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 month and last two weeks 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 weeks of pregnancy were similar. **OR for PTB [Lower CI, Upper CI]** **First month 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 weeks 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**

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Hwang and Jaakkola (2008) **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) **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 weeks)	**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 month:** 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 month prior to birth:** All of Sydney : 0.96 (0.88-1.04) Within 5km of site : 1.00 (0.86-1.15) **3 months prior to birth:** All of Sydney : 0.99 (0.90-1.09) Within 5km of site : 1.11 (0.94-1.31)
Author: Lee et al. (2003a) **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 weeks)	**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) **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. (2004a) **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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lin et al. (2004b) **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:** 92288 full term live singleton births (>37 weeks) within 3km 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.
Author: Liu et al. (2003) **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 month: 1.01 (0.93-1.09) Last month: 0.96 (0.88-1.04) **OR for PTB [Lower CI, Upper CI]** First month : 0.95 (0.89-1.01) Last month : 1.08 (1.01-1.15) **OR for IUGR [Lower CI- Upper CI]** First month : 1.06 (1.01-1.10) Last month : 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) **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 month of pregnancy. (All results presented in Figures)
Author: Maisonet et al. (2001) **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 weeks)	**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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Mannes et al. (2005) **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 weeks 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 month 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 trimester : -22.88 (-44.58 to -1.18) One month 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 month 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 month prior to birth : 1.10 (0.96-1.27)
Author: Medeiros et al. (2005) **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 weeks)	**Averaging Time:** 24-h **Mean (SD) unit:** Daily mean shown in Figure (see paper) **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** 1 ppm **Regression co-efficient 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: Parker et al. (2005) **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 weeks) within 5 miles 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)
Author: Ritz et al. (2000) **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 26-44 weeks 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 weeks prior to birth : 1.04 (0.99-1.10) 1st month of pregnancy : 1.04 (0.99-1.09) **Adjusted for various risk factors** 6 weeks prior to birth : 1.06 (1.02-1.10) 1st month of pregnancy : 1.01 (0.97-1.04)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ritz et al. (2002) **Period of Study:** 1987 - 1993 **Location:** Southern California	**Health Outcome:** Birth defects (heart defects & 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 month of pregnancy. **Aortic artery & 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 & 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) **Period of Study:** 1989 - 2000 **Location:** Southern California	**Health Outcome:** Post-neonatal 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 weeks prior to death, 1 month prior to death, 2 months prior to death, 6 months prior to death **All causes:** 2 weeks prior to death : 1.14 (1.03-1.25) 2 months prior to death : 1.11 (1.06-1.16) **SIDS:** 2 months prior to death : 1.19 (1.10-1.28) **Term/normal weight births** **2 months 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 months 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)
Author: Ritz et al. (2007) **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 weeks 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) **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)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Tsai et al. (2006b) **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) **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 miles 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 weeks 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:** Less than 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 weeks prior to birth:** Less than 1 mile: 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:** Less than 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) **Period of Study:** 1999 - 2002 **Location:** U.S. counties with >250,000 residents	**Health Outcome:** Post-neonatal 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 months 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. (2004b) **Period of Study:** 1994 - 2000 **Location:** Taipei, Taiwan	**Health Outcome:** Post-neonatal 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: Chen et al. (1999) **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	**Pollutant:** CO **Averaging Time:** 1-h maximum; 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** 1-h maximum: (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 maximum** -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 maximum** 1.2 (19.48); 1 -1.44 (18.57); 2 20.96 (15.67); 7
Author: Chen et al. (2000) **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 maximum **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
Author: de Hartog et al. (2003) **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:** Non-smoking individuals with CHD: Amsterdam: 37 Erfurt: 47 Helsinki: 47 **Age Groups Analyzed:** ≥ 50	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Amsterdam: 0.6 mg/m³ Erfurt: 0.4 mg/m³ Helsinki: 0.4 mg/m³ **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/m³ **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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Delfino et al. (2003) **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	**Pollutant:** CO **Averaging Time:** 1-h maximum; 8-h maximum **Mean (SD) unit:** 1-h maximum: 7.7 (3.1) ppb 8-h maximum: 5.0 (2.0) ppb **Range (Min, Max):** 1-h maximum: (2, 17) 8-h maximum: (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-maximum** **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 maximum** **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) **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	**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)
Author: Fischer et al. (2002) **Period of Study:** NR **Location:** Utrecht, Netherlands	**Health Outcome:** Lung function (FVC, FEV_1, PEF, MMEF) **Study Design:** Panel study **Statistical Analyses:** Restricted maximum likelihood linear model **Population:** 68 children **Age Groups Analyzed:** 10-11	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 921 µg/m³ **Range (Min, Max):** (319, 1540) **Copollutant:** PM_{10}; BS; NO_2; NO	**Increment:** 100 µg/m³ **mL (SE); lag:** **FVC:** 0.5 (0.4); 1; 0.1 (0.2); 2 **FEV_1:** -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

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lagorio et al. (2006) **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 Asthma panel: 18-64 IHD panel: 40-64 **Notes:** Asthma panel was restricted to never smokers, while COPD and IHD panels include former smokers if smoking cessation occurred at least 1 year 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 **FEV_1 (% 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 **FEV_1 (% 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 **FEV_1 (% of predicted)** 0.204 (0.120); 0 0.114 (0.142); 0-1 0.159 (0.194); 0-2
Author: Park et al. (2002) **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. (2005a) **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	**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) **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 non-smoking 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 PM1: 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) **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	**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: FEV_1** **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) **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	**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:** NO_2; TSP; $PM_{2.5}$	**The study did not present quantitative results for CO.**
Author: Rodriguez et al. (2007) **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	**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) **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	**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/m3 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/m3 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) **Period of Study:** 11/11/1999 – 3/31/2000; 11/1/2000 – 3/16/2001 **Location:** Denver, CO	**Health Outcome:** Lung function (FEV_1, 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 years of tobacco use, airflow limitation with FEV_1 of less than 70% of predicted value, and FEV_1/ FVC ratio of less than 60% 2nd winter: 18 with a history of more than 10 pack years of tobacco use, airflow limitation with FEV_1 of less than 70% of predicted value, and FEV_1/ FVC ratio of less than 60% **Age Groups Analyzed:** ≥ 40	**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) **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	**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) **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 maximum likelihood linear model **Population:** 126 children **Age Groups Analyzed:** 8-13 **Notes:** The study was only conducted for a two month 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) **Period of Study:** 2/1994 – 4/1994 **Location:** Kuopio, Finland	**Health Outcome:** Exercise induced bronchial responsiveness; Lung function (FVC, FEV_1, MMEF, AEFV) **Study Design:** Panel study **Statistical Analyses:** Linear regression **Population:** 33 children with chronic respiratory symptoms **Age Groups Analyzed:** 7-12	**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 $PNC_{0.01-0.03}$: r = 0.81 $PNC_{0.03-0.1}$: r = 0.87 $PNC_{0.1-0.3}$: r = 0.71 $PNC_{0.3-1.0}$: r = 0.60 $PNC_{1.0-3.2}$: r = 0.84 $PNC_{3.2-10}$: 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) **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	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.9 mg/m^3 **Range (Min, Max):** (0.3, 3.0) **Copollutant correlation:** $NC_{0.01-0.1}$: r = 0.66 $NC_{0.1-0.5}$: r = 0.79 $NC_{0.5-2.5}$: r = 0.46 $MC_{0.1-0.5}$: r = 0.66 $MC_{0.01-2.5}$: 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) **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	**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: Anderson et al. (2001) **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 15-64 ≥ 65	**Pollutant:** CO **Averaging Time:** Maximum 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Andersen et al. (2007) **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; ≥ 65	**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) **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 15-64 ≥ 65	**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
Author: Bedeschi et al. (2007) **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:** <15	**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.**

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Bell et al. (2008) **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
Author: Bellini et al. (2007) **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/m³ **% 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) **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 3-5 6-13 14-19 0-19	**Pollutant**: CO **Averaging Time:** Maximum 8-h avg **Mean (SD) unit:** 4.8 (2.3) ppm **Range (Min, Max):** (0.6, 19.1) **Copollutant:** correlationCopollutant: 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Burnett et al. (1999) **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**: **Multi-pollutant 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**: **Multi-pollutant 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) **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	**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
Author: Cakmak et al. (2006b) **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) **Period of Study:** 1996-2004 **Location:** Kaohsiung, Taiwan	**Hospital Admissions** **Health Outcome (ICD9):** Pneumonia (480-486) **Study Design:** Bi-directional 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 ℃: 1.18 (1.14-1.23); 0-2 CO, <25 ℃: 1.47 (1.41-1.53); 0-2 CO, PM_{10}, ≥ 25 ℃: 1.15 (1.11-1.2); 0-2 CO, PM_{10}, <25 ℃: 1.28 (1.21-1.35); 0-2 CO, SO_2, ≥ 25 ℃: 1.22 (1.17-1.27); 0-2 CO, SO_2, <25 ℃: 1.49 (1.42-1.56); 0-2 CO, NO_2, ≥ 25 ℃: 1.2 (1.15-1.27); 0-2 CO, NO_2, <25 ℃: 1.01 (0.95-1.08); 0-2 CO, O_3, ≥ 25 ℃: 1.16 (1.12-1.2); 0-2 CO, O_3, <25 ℃: 1.44 (1.38-1.5); 0-2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Cho et al. (2000) **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: Farhat et al. (2005) **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:** Maximum 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
Author: Fung et al. (2006) **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. Bi-directional case-crossover **Statistical Analyses:** 1. Dewanji and Moolgavkar 2. Poisson 3. Conditional logistic regression **Age Groups Analyzed:** ≥ 65	**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 **Bi-directional 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Fusco et al. (2001) **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	**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 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 (2000a) **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 <5	**Pollutant:** CO **Averaging Time:** Maximum 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hajat et al. (1999) **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 15-64 $\geq$ 65	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** All year: 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 **$\geq$ 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 **$\geq$ 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 **$\geq$ 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 **$\geq$ 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 $\geq$ 65 & Warm Season: 15.60% (3.10-29.60); 2 $\geq$ 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 $\geq$ 65 & Warm Season: 1.00% (-1.60 to 3.80); 2 $\geq$ 65 & Cold Season: -2.20% (-6.50 to 2.40); 3
Author: Hajat et al. (2002) **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 15-64 $\geq$ 65	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** **All year:** 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 **$\geq$ 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 **$\geq$ 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 **$\geq$ 65:** 5.80% (2.40 to 9.30); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hapcioglu et al. (2006) **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) **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:** Maximum 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) **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 15-64 ≥ 65	**Pollutant:** CO **Averaging Time:** Maximum 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
Author: Ito et al. (2007) **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:** Maximum 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Karr et al. (2007) **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 weeks -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 bronchitis**: 1 (0.97-1.03) **Increment:** 960 ppb **Chronic broncholitis**: 1 (0.97-1.03)
Author: Karr et al. (2006) **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 weeks – 1 year	**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 week and in the same month 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 weeks**: 0.86 (0.68-1.1); 1 **29 1/7 – 34 weeks**: 1 (0.86-1.15); 1 **34 1/7 – 37 weeks**: 0.95 (0.87-1.04); 1 **37 1/7 – 44 weeks**: 1 (0.97-1.03); 1 **Increment:** 1400 ppb **Age Group:** **Overall:** 0.97 (0.94-1); 4 **25-29 weeks**: 0.93 (0.72-1.2); 4 **29 1/7 – 34 weeks**: 0.89 (0.77-1.03); 4 **34 1/7 – 37 weeks**: 0.98 (0.90-1.08); 4 **37 1/7 – 44 weeks**: 0.97 (0.94-1); 4
Author: Kim et al. (2007) **Period of Study:** 2002 **Location:** Seoul, Korea	**Hospital Admissions** **Health Outcome (ICD10):** Asthma (J45 and J46) **Study Design**: Bi-directional case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All Ages	**Pollutant**: CO **Averaging Time:** Maximum 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Kontos et al. (1999) **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	**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) **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:** <15	**Pollutant:** CO **Averaging Time:** 1-h maximum **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 years 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
Author: Lee et al. (2006) **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	**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. (2007b) **Period of Study:** 1996-2003 **Location:** Kaohsiung, Taiwan	**Hospital Admissions** **Health Outcome (ICD9):** COPD (490-492, 494, 496) **Study Design:** Bi-directional 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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lin et al. (1999) **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:** <13	**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
Author: Lin et al. (2003) **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	**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. (2004c) **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	**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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lin et al. (2005) **Period of Study:** 1998-2001 **Location:** Toronto, Canada	**Hospital Admissions** **Health Outcome (ICD9):** Respiratory Infections (464, 466, and 480-487) **Study Design:** Bi-directional case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** <15	**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
Author: Linn et al. (2000) **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, ≥ 30	**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) **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 15-64 ≥ 65	**Pollutant**: CO **Averaging Time:** 1-h maximum **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) **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	**Pollutant**: CO **Averaging Time:** Maximum 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) **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 stepwise 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) **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; >64	**Pollutant**: CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.16 (1.51) mg/m³ **Range (Min, Max):** (0, 15.7) **Copollutant:** NR	This study did not provide quantitative results for CO.
Author: Migliaretti et al. (2007) **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 15-64 >64	**Pollutant**: CO **Averaging Time:** 8-h median **Median (SD) unit:** 3.36 (1.57) mg/m³ **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 (2000a) **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 20-64 ≥ 65	**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; / I: 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 (2003b) **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	**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) **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 1-3 3-6 6-12 12-18	**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) **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:** <18	**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) **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	**Pollutant:** CO **Averaging Time:** 1-h maximum **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
Author: Sheppard et al. (1999) **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	**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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Slaughter et al. (2005) **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
Author: Steib et al. (2007) **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 maximum **Mean (SD) unit:** All year: 0.5 (0.3) ppm May-September: 0.6 (0.3) ppm All year: 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 **% Increase (Lower CI, Upper CI); lag:** All Respiratory Illnesses **Increment:** 0.5 ppm All Year: -3.40; 7 **Increment:** 1.7 ppm May- September: -5.70
Author: Sun et al. (2006) **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; 16-55	**Pollutant:** CO **Averaging Time:** Monthly **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Correlation Coefficient:** **Asthma** **Age Group:** **<16:** 0.653 **16-55:** 0.425

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Tenias et al. (2002) **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	**Pollutant**: CO **Averaging Time:** 24-h avg 1-h maximum **Mean (SD) unit:** 24-h avg All year: 3.1 mg/m^3 Warm Months: 2.5 mg/m^3 Cold Months: 3.7 mg/m^3 1-h avg All year: 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 maximum: (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 maximum** 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) **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; NOx (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.
Author: Tolbert et al. (2007) **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 maximum **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) **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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Tsai et al. (2006a) **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) **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; >65	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.5 (0.7) ug/m³ **Range (Min, Max):** (0.3, 3.5) **Copollutant: correlation** NO_2: r = 0.62 PM_{10}: r = 0.70	**Increment:** 1mg/m³ **% 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
Author: Villeneuve et al. (2006b) **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	**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) **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; <2; 2-5; >5	**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) **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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Yang et al. (2007) **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
Author: Yang et al. (2005) **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	**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) **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; ≥ 65	**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. (2004b) **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	**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) **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) **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	**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) **Period of Study:** 10/1995 – 5/1996 **Location:** Taiwan	**Health Outcome:** Asthma **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Population:** 331,686 non-smoking children **Age Groups Analyzed:** Middle-school children (mean age: 13.8)	**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)
Author: Hirsch et al. (1999) **Period of Study:** Population: 9/1995-6/1996 Air: 4/1994 – 4/1995 **Location:** Dresden, Germany	**Health Outcome:** Asthma symptoms in the past 12 months (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	**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 µg/m^3 **Prevalence Odds Ratio (Lower CI, Upper CI); lag:** **Symptoms in the past 12 months: 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: FEV$_1$ <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: FEV$_{25-75}$% <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 months: 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

Study	Design	Concentrations	Effect Estimates (95% CI)
			Children were defined as those children with specific IgE to aeroallergens ≤ 0.7 kU-L-1.
Author: Hwang et al. (2006) **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	**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)
Author: Hwang et al. (2005) **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	**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. (2003c) **Period of Study:** 10/1995-5/1996 **Location:** Taiwan	**Health Outcome:** Allergic rhinitis **Study Design:** Cohort **Statistical Analyses:** Multiple logistic regression **Population:** 331,686 non-smoking children **Age Groups Analyzed:** 12-14	**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) **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	**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) **Period of Study:** 1989 – 2000 **Location:** San Joaquin Valley, CA	**Health Outcome:** Lung function (FVC, FEV_1, PEF, FEF_{25-75}, FEV_1/FVC, FEF_{25-75}/FVC, FEF_{25}, FEF_{75}) **Study Design:** Cohort **Statistical Analyses:** 1. DSA algorithm 2. GEE **Population:** 232 asthmatic children **Age Groups Analyzed:** 6-11	**Pollutant:** CO **Averaging Time:** 8-h maximum 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 maximum): r = -0.40 PM_{10} (24-h avg): r = 0.05 **Prenatal** CO (8-h maximum): r = 0.52 NO_2 (24-h avg): r = 0.37 O_3 (8-h maximum): r = -0.16 PM_{10} (24-h avg): r = -0.05	**Increment:** NR **Effect Size per IQR Increase in Pollutant (SE):** **FEF_{25-75}:** 24-h avg CO exposure during 1st trimester 0.90% (0.0113) **FEV_1/FVC** Daily maximum CO exposure during ages 0 to 3 -2.50% (0.0016) **FEF_{25-75}/FVC** 24-h avg CO exposure during ages 0 to 6 and diagnosed with asthma <2 years old -4.80% (0.0446) **FEF_{25}** 24-h avg CO exposure during ages 0 to 6 and diagnosed with asthma <2 years 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) **FEF_{25-75}** Lifetime 24-h avg CO exposure -0.94454 (0.3975) **FEF_{25-75}/FVC** -0.1090 (0.0303) **FEV_1/FVC** Prenatal 8-h maximum CO exposure: 0.1711 (0.0653) Lifetime 1-h maximum CO exposure: -0.3242 (0.0919) 24-h avg CO exposure during ages 0-3 and diagnosed with asthma <2 years old: -0.1814 (0.0599) **FEF_{25}** 24-h avg CO exposure during ages 0-6 and diagnosed with asthma <2 years old: -1.0460 (0.1953) **FEF_{75}** Lifetime 8-h maximum CO exposure: -0.4214 (0.1423)
Author: Singh et al. (2003) **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	**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.**
Author: Wang et al. (1999) **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	**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)

Table C-7.   Studies of short-term CO exposure and mortality.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Anderson et al. (2001) **Period of Study:** 10/1994 – 12/1996 **Location:** West Midlands, United Kingdom	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<800); Cardiovascular (390-459); Respiratory (460-519) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Maximum 8-h moving avg **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) **Period of Study:** 1996 – 2002 **Location:** 15 Italian cities	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<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: Biggeri et al. (2005) **Period of Study:** 1990-1999 **Location:** 8 Italian Cities (Turin, Milan, Verona, Bologna, Ravenna, Florence, Rome, and Palermo)	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<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:** Maximum 8-h moving average **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) **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	**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)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Bremner et al. (1999) **Period of Study:** 1/1992–12/1994 **Location:** London, U.K.	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<800); Cardiovascular (390-459); Respiratory (460-519) **Study Design:** Time-series **Statistical Analyses:** Poisson, cubic splines **Age Groups Analyzed:** All ages 0-64 ≥ 65 65-74 ≥ 75	**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
Author: Burnett et al. (2000) **Period of Study:** 1986-1996 **Location:** 8 Canadian cities	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<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 non-accidental 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) **Period of Study:** 1981 – 1999 **Location:** 12 Canadian cities	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Cakmak et al. (2007) **Period of Study:** 1/1997 – 12/2003 **Location:** Chile – 7 cities	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental) (<800); Cardiovascular diseases (390-459); Respiratory diseases (460-519) **Study Design:** Time-series **Statistical Analyses:** Poisson; Random effects regression model **Age Groups Analyzed:** All ages ≤ 64 65 – 74 75 – 84 ≥ 85	**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:** **Non-accidental:** 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; *l* 4.76% (2.19); 0-5 **Age Group: 65-74** 6.24% (3.17); 1; *l* 8.12% (3.88); 0-5 **Age Group: 75-84** 8.64% (4.82); 1; *l* 13.12% (5.12); 0-5 **Age Group: ≥ 85** 8.58% (4.45); 1; *l* 13.20% (4.82); 0-5 **April-September** 7.09% (4.02); 1; *l* 9.65% (4.50); 0-5 **October-March** 5.45% (1.14); 1; *l* 7.80% (1.89); 0-5 **Cardiac** 7.79% (4.56); 1; *l* 11.22% (4.8); 0-5 **Respiratory** 12.93% (5.78); 1; *l* 21.31% (6.34); 0-5

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Chock et al. (2000) **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 >75	**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 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) **Period of Study:** 1988 – 1996 **Location:** Santiago, Chile	**Health Outcome (ICD9):** Mortality: All causes (non-accidental) (<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 year: 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) **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	**Pollutant:** CO **Averaging Time:** Maximum 8-h moving avg **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) **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 >75	**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. (2003b) **Period of Study:** 1987 – 1994 **Location:** 90 U.S. cities (NMMAPS)	**Health Outcome (ICD9):** Mortality: All-cause (non-accidental); 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) **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; Maximum 8-h avg **Median (SD) unit:** 24-h avg: 1.4 (1.0) ppm Maximum 8-h avg: 2.1 (1.6) ppm **Range (Min, Max):** 24-h avg: (0.0, 7.6) Maximum 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) **Period of Study:** 1986 – 1994 **Location:** The Netherlands	**Health Outcome (ICD9):** Mortality: Non-accidental (<800); Pneumonia (480-486); COPD (490-496); Cardiovascular (390-448) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** <45 45-64 65-74 ≥ 75	**Pollutant:** CO **Averaging Time:** 24-h avg **Median (SD) unit:** 406 µg/m³ **Range (Min, Max):** (174, 2620) **Copollutant:** PM_{10}; BS; O_3; NO_2; SO_2	**Increment:** 1,200 µg/m³ **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) **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	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 2.4 (1.0) mg/m³ **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) **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	**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) **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; ≥ 65	**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) **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	**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) **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	**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. (2000b) **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 <5	**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) **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) **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/m³ **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) **Period of Study:** 1986 – 1994 **Location:** The Netherlands	**Health Outcome (ICD9):** Mortality: Pneumonia (480-486); COPD (490-496); Cardiovascular diseases (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/m³ Four Major Cities: 589 µg/m³ **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/m³ Weekly avg (0-6): 1200 µg/m³ **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) **Period of Study:** 1976-1990 **Location:** Tokyo, Japan	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800) **Study Design:** Time-series **Statistical Analyses:** Poisson **Age Groups Analyzed:** ≥ 65	**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)
Author: Hong et al. (2002b) **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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hong et al. (1999a) **Period of Study:** 1/1995 - 12/1995 **Location:** Inchon, Korea	**Health Outcome (ICD9):** Mortality: Cardiovascular (400-440); Respiratory (460-519); Non-accidental 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. (2002a) **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. (1999b) **Period of Study:** 1/1995 - 8/1996 **Location:** Inchon, South Korea	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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) **Period of Study:** 1976-1995 **Location:** London, England	**Health Outcome (ICD9):** Mortality: Non-accidental 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.
Author: Kettunen et al. (2007) **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	**Pollutant:** CO **Averaging Time:** Maximum 8-h moving avg **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; *I* -0.63 (-4.39 to 3.28); 1; -2.69 (-6.46 to 1.24); 2; *I* -0.19 (-3.93 to 3.69); 3 **Warm Season** 3.95 (-3.78 to 12.30); 0; *I* 8.33 (0.63 to 16.63); 1; 6.97 (-0.59 to 15.11); 2; *I* 7.54 (-0.05 to 15.71); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Klemm et al. (2004) **Period of Study:** 8/1998-7/2000 **Location:** Fulton County and DeKalb County, GA (ARIES)	**Health Outcome (ICD9):** Mortality: Non-accidental (<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; ≥ 65	**Pollutant:** CO **Averaging Time:** 1-h maximum **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: Kwon et al. (2001) **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 55-64 65-74 75-84 ≥ 85	**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 weeks: 1.088 (0.907-1.306); 0 >4 weeks: 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. (2007c) **Period of Study:** 1/2000-12/2004 **Location:** Seoul, Korea	**Health Outcome (ICD10):** Mortality: Non-accidental (A00-R99) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Maximum 8-h moving avg **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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lipfert et al. (2000b) **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:** Stepwise regression **Age Groups Analyzed:** <65 ≥ 65	**Pollutant:** CO **Averaging Time:** 24-h avg; 1-h maximum **Mean (SD) unit:** Camden: 24-h avg: 0.75 (0.40) ppm Philadelphia: 24-h avg: 0.63 (0.40) ppm 1-h maximum: 1.44 (1.04) **Range (Min, Max):** Camden: (0.10, 3.8) Philadelphia: 24-h avg: (0.10, 3.3) 1-h maximum: (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
Author: Lippmann et al. (2000) **Period of Study:** 1985-1990 1992-1994 **Location:** Detroit, MI and Windsor, ON	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Circulatory (390-459); Respiratory (460-519) **Study Design:** Time-series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** ≥ 65	**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

Study	Design	Concentrations	Effect Estimates (95% CI)
			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 **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. (2005a) **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	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NOx; PM$_{10}$ **Notes:** Quintiles represent the following mean CO concentrations and category limits: 5: 482 µg/m³ (≥ 455) 4: 443 µg/m³ (≥ 433 to <455) 3: 426 µg/m³ (≥ 419 to <433) 2: 405 µg/m³ (≥ 387 to <419) 1: 360 µg/m³ (<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. (2005b) **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	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Quintile: 5: 482 µg/m³; 4: 443 µg/m³; 3: 426 µg/m³; 2: 405 µg/m³; 1: 360 µg/m³ **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/m³ (≥ 455) 4: 443 µg/m³ (≥ 433 to <455) 3: 426 µg/m³ (≥ 419 to <433) 2: 405 µg/m³ (≥ 387 to <419) 1: 360 µg/m³ (<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) **Period of Study:** 1995-1997 **Location:** Phoenix, AZ	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Cardiovascular (390-449) **Study Design:** Time-series **Statistical Analyses:** Poisson **Age Groups Analyzed:** >65	**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
Author: Moolgavkar et al. (2000b) **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$_3$:	**Increment:** 1 ppm **% Change (Lower CI, Upper CI); lag:** **CVD Mortality** **Cook County** CO -1.07 (-2.67, 0.54); 0; *I* 1.25 (-0.36, 2.87); 1; 1.49 (-0.09, 3.07); 2; *I* 1.90 (0.32, 3.48); 3; 1.44 (-0.16, 3.03); 4; *I* 0.72 (-0.89, 2.32); 5 **Los Angeles County** CO 3.47 (2.94, 4.00); 0; *I* 3.93 (3.41, 4.46); 1; 4.08 (3.56, 4.60); 2; *I* 3.76 (3.24, 4.28); 3; 2.91 (2.37, 3.44); 4; *I* 2.63 (2.09, 3.17); 5 CO, PM$_{10}$ 2.27 (0.88, 3.66); 0; *I* 4.33 (2.96, 5.69); 1; 4.72 (3.38, 6.05); 2; *I* 4.26 (2.90, 5.63); 3; 2.49 (1.10, 3.88); 4; *I* 5.93 (4.60, 7.27); 5 CO and PM$_{2.5}$ 0.43 (-1.35, 2.20); 0; *I* 2.88 (1.16, 4.60); 1; 4.65 (2.93, 6.37); 2; *I* 5.93 (4.20, 7.65); 3; 3.88 (2.13, 5.63); 4; *I* 5.85 (4.12, 7.58); 5 **Maricopa County** CO 0.81 (-0.79, 2.39); 0; *I* 2.20 (0.61, 3.79); 1;

Study	Design	Concentrations	Effect Estimates (95% CI)
		Cook: r = -0.28; LA: r = -0.52; Maricopa: r = -0.61	3.05 (1.49, 4.61); 2; *I* 3.78 (2.27, 5.28); 3; 3.73 (2.27, 5.19); 4; *I* 2.25 (0.76, 3.72); 5 **COPD Mortality** **Cook County** CO -2.65 (-7.05, 1.75); 0; *I* 2.80 (-1.60, 7.19); 1; 0.98 (-3.34, 5.31); 2; *I* 2.20 (-2.12, 6.53); 3; 1.31 (-3.06, 5.68); 4; *I* 1.59 (-2.78, 5.97); 5 **Los Angeles County** CO 3.78 (2.31, 5.25); 0; *I* 5.23 (3.78, 6.69); 1; 5.71 (4.26, 7.17); 2; *I* 5.42 (3.95, 6.89); 3; 4.01 (2.51, 5.50); 4; *I* 3.82 (2.31, 5.33); 5 **Maricopa County** CO 1.29 (-2.19, 4.76); 0; *I* 4.63 (1.17, 8.09); 1; 0.07 (-3.36, 3.50); 2; *I* 3.00 (-0.30, 6.30); 3; 6.21 (3.02, 9.40); 4; *I* 3.27 (0.04, 6.50); 5 **Cerebrovascular Disease Mortality** **Cook County** -0.41 (-3.30, 2.47); 0; *I* 3.13 (0.23, 6.02); 1; 2.12 (-0.73, 4.97); 2; *I* 1.00 (-1.85, 3.86); 3; 2.50 (-0.36, 5.37); 4; *I* 1.88 (-1.00, 4.76); 5 **Los Angeles County** 3.31 (2.32, 4.31); 0; *I* 3.88 (2.89, 4.87); 1; 3.23 (2.25, 4.22); 2; *I* 2.65 (1.66, 3.65); 3; 2.11 (1.11, 3.12); 4; *I* 2.04 (1.02, 3.06); 5 **Maricopa County** 0.26 (-2.65, 3.16); 0; *I* 3.50 (0.60, 6.41); 1; 3.52 (0.66, 6.38); 2; *I* 4.61 (1.85, 7.37); 3; 4.78 (2.10, 7.46); 4; *I* 5.15 (2.45, 7.84); 5 **Notes:** Total Mortality effect estimates were not presented quantitatively.
Author: Moolgavkar et al. (2003b) **Period of Study:** 1987-1995 **Location:** Cook County, Illinois & Los Angeles County, California	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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; *I* 2.5% (5.4); 1; *I* 1.2% (2.6); 2; 1.5% (3.2); 3; *I* 1.1% (2.5); 4; *I* 0.6% (1.3); 5 **CO, PM_{10}:** -0.5% (-1.0); 0; *I* 2.2% (4.3); 1; *I* 1.1% (2.2); 2; 1.0% (1.9); 3; *I* 1.1% (2.1); 4; *I* 1.4% (2.7); 5 **Total Mortality Los Angeles County** **CO:** 1.3% (7.4); 0; *I* 1.9% (10.5); 1; *I* 1.6% (8.9); 2; 1.4% (8.1); 3; *I* 1.0% (5.9); 4; *I* 0.7% (4.1); 5 **CO, PM_{10}:** 0% (0); 0; *I* 2.2% (4.8); 1; *I* 1.4% (3.1); 2; 0.8% (1.8); 3; *I* 0.7% (1.6); 4; *I* 1.3% (3.0); 5 **CO, $PM_{2.5}$:** -0.1% (-1.5); 0; *I* 1.5% (2.5); 1; *I* 2.4% (3.8); 2; 0.3% (0.5); 3; *I* 1.6% (2.8); 4; *I* 1.5% (2.6); 5 **Total Mortality (Season-specific) Cook County** **Spring (CO):** 0.8% (0.9); 0; *I* 2.4% (2.9); 1; *I* 0% (0); 2; 1.2% (1.5); 3; *I* 0.8% (1.0); 4; *I* -0.1% (-0.2); 5 **Summer (CO):** 1.2% (1.0); 0; *I* 3.6% (3.0); 1; *I* 4.2% (3.6); 2; -0.3% (-0.2); 3; *I* -1.1% (-1.0); 4; *I*-0.7% (-0.6); 5 **Fall (CO):** 1.2% (1.5); 0; *I* 2.1% (2.7); 1; *I* 0% (0); 2; 0% (0); 3; *I*-0.5% (-0.6); 4; *I* -0.7% (-0.9); 5 **Winter (CO):** -0.7% (-1.0); 0; *I* 1.8% (2.3); 1; *I* -0.2% (-0.3); 2; 0.5% (0.6); 3; *I* 1.2% (1.5); 4; *I* 1.0% (1.3); 5 **Los Angeles County** **Total Mortality (Season-specific)** **Spring (CO):** 3.6% (6.3); 0; *I* 3.5% (6.2); 1; *I* 1.9% (3.4); 2; 0.6% (1.0); 3; *I* -0.5% (-0.8); 4; *I* -0.7% (-1.2); 5

Study	Design	Concentrations	Effect Estimates (95% CI)
			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, PM2.5: -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
			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) **Period of Study:** 1989-1992 **Location:** Coachella Valley, California	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Respiratory (460-519); Cardiovascular (393-440) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM; LOESS **Age Groups Analyzed:** >50	**Pollutant:** CO **Averaging Time:** 1-h maximum **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

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Penttinen et al. (2004) **Period of Study:** 1988-1996 **Location:** Helsinki, Finland	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Respiratory (460-519); Cardiovascular (393-440) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages 15-64 years 65-74 years ≥ 75	**Pollutant:** CO **Averaging Time:** Maximum 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 Morality** -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. (2000a) **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 Cardiovascular Disease 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
Author: Rainham et al. (2003) **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) **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. (2000b) **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) **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) Rome: (2.5, 5.9) Stockholm: (0.5, 1.2)	**Increment:** 1 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** **Non-accidental mortality** **8 Degrees of Freedom per year** **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)
		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 **Population >75 years of age (%):** 25th Percentile: 0.58% (0.25-0.92); 0-1 75th Percentile: 0.94% (0.64-1.24); 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
			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 years 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) **Period of Study:** 1989-1995 **Location:** Spokane, WA	**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:** 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) **Period of Study:** 1996-1998 **Location:** Sao Paulo, Brazil	**Health Outcome (ICD10):** Mortality: Myocardial Infarction (I.21) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** 35-109	**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) **Period of Study:** 1/1995 - 6/2001 **Location:** Spokane, WA	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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 :** PM1: 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) **Period of Study:** 1985-2000 **Location:** All locations	**Health Outcome (ICD9):** Mortality: Non-accidental **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. (2006) **Period of Study:** 9/1995-8/2001 **Location:** Erfurt, Germany	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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:** $MC_{0.1-0.5}$: r = 0.58; $MC_{0.01-2.5}$: 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) **Period of Study:** 1990-1995 **Location:** Barcelona, Spain	**Health Outcome (ICD9):** Mortality: COPD (491, 492, 494, 496) **Study Design:** Bi-directional case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** >35	**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 µg/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) **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 **Study population:** Asthmatic individuals: 5,610	**Pollutant:** CO **Averaging Time:** 24-h avg **Median (SD) unit:** 7.7 µg/m^3 **Range (Min, Max):** (0.6, 66.0) **Copollutant:** PM_{10}; BS; NO_2; O_3; SO_2	**Increment:** 7.2 µg/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. (2003a) **Period of Study:** 1994-2000 **Location:** Kaohsiung, Taiwan	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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 (non-accidental): 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. (2006b) **Period of Study:** 1994-2000 **Location:** Kaohsiung, Taiwan	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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
Author: Vedal et al. (2003) **Period of Study:** 1/1994-12/1996 **Location:** Vancouver, BC, Canada	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<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.**

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Villeneuve et al. (2003) **Period of Study:** 1986-1999 **Location:** Vancouver, BC, Canada	**Health Outcome (ICD9):** Mortality: Non-accidental (<800); Cardiovascular (401-440); Respiratory (460-519); Cancer (140-239) **Study Design:** Time-series **Statistical Analyses:** Poisson, natural splines **Age Groups Analyzed:** ≥ 65	**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; *I* -0.3% (-2.2 to 1.7); 0; 0.6% (-1.3 to 2.6); 1; *I* 0.5% (-1.4 to 2.5); 2 **Cardiovascular** 2.3% (-1.6 to 6.3); 0-2; *I* 1.6% (-1.5 to 4.7); 0; 1.2% (-2.0 to 4.5); 1; *I* 1.5% (-1.5 to 4.4); 2 **Respiratory** -1.0% (-7.3 to 5.8); 0-2; *I* 1.3% (-4.4 to 7.3); 0; -0.1% (-5.3 to 5.4); 1; -*I* 2.8% (-7.8 to 2.6); 2 **Cancer** -2.8% (-7.6 to 2.4); 0-2; *I* -3.0% (-6.9 to 1.1); 0; -1.6% (-5.6 to 2.4); 1; *I* -0.5% (-4.7 to 3.8); 2
Author: Wichmann et al. (2000) **Period of Study:** 9/1995 - 12/1998 **Location:** Erfurt, Germany	**Health Outcome (ICD9):** Mortality: Non-accidental (<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/m³ **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. (2004a) **Period of Study:** 1994-1998 **Location:** Taipei, Taiwan	**Health Outcome (ICD9):** Mortality: Non-accidental (<800); Circulatory (390-459); Respiratory (460-519) **Study Design:** Bi-directional 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: Lipfert et al. (2000b) **Period of Study:** 1975-1996 **Location:** 32 Veterans Hospitals, USA	**Mortality** **Health Outcome (ICD9):** Non-accidental **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.
Author: Lipfert and Morris (2002) **Period of Study:** 1960-1997 **Location:** U.S. counties	**Mortality** **Health Outcome (ICD9):** Non-accidental **Study Design:** Ecological/ cross-sectional **Statistical Analyses:** Staged regression **Age Groups Analyzed:** 15-44 45-64 65-74 75-84 ≥ 85	**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 **Range (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)

Study	Design	Concentrations	Effect Estimates (95% CI)
			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** 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**

Study	Design	Concentrations	Effect Estimates (95% CI)
			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)
Author: Lipfert et al. (2006b) **Period of Study:** 1976-2001 **Location:** 32 Veterans Hospitals, USA	**Mortality** **Health Outcome (ICD9):** Non-accidental **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/km2	**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)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lipfert et al. (2006a) **Period of Study:** 1997-2002 **Location:** 32 Veterans Hospitals, USA	**Mortality** **Health Outcome (ICD9):** Non-accidental **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-: $r = -0.088$ $\sum PM_{2.5}$ 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) **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 cardiovascular disease **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** ≥ 30	**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)
Author: Miller et al. (2007) **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 cardiovascular disease **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** 50-79	**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) **Period of Study:** 1980-1998 **Location:** All 50 States, Washington DC, and Puerto Rico (ACS-CPS-II)	**Mortality** **Health Outcome (ICD9):** Total (non-accidental) (<800); Lung Cancer (162); Cardiopulmonary (401-440, 460-519) **Study Design:** Prospective cohort **Statistical Analyses:** Cox proportional hazards model **Age Groups Analyzed:** ≥ 30	**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.**

Annex D. Controlled Human Exposure Studies

Table D-1.   Controlled human exposure studies.

Study	Subjects	Exposure	Findings
Adir et al. (1999)	15 healthy non-smoking males; 22-34 years old	Subjects exposed to both CO and room air for 3 min 45 sec. Actual inhaled CO concentration not provided. Subjects exposed to CO concentration required to produce a venous COHb of 4-6%. Exposures were separated by 1 month with the order of exposure randomly assigned.	Exposure to CO resulted in a decrease in post-exposure exercise duration (Bruce protocol) relative to clean air exposure in 13 out of 15 subjects (p=0.0012). Statistically significant decreases in metabolic equivalent units (METs) were also reported following CO exposure (p = 0.0001). No CO-induced changes in heart rate (HR), BP, ECG parameters, or myocardial perfusion were observed.
Bathoorn et al. (2007)	19 former smokers with COPD; 18 males/1 female; 66-70 years old	Exposures to both CO and room air conducted for 2 h on each of four consecutive days in a randomized crossover design. 9 subjects were exposed to 100 ppm and 10 subjects were exposed to 125 ppm. CO and room air exposures were separated by at least 1 week.	Following the fourth 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 two of these patients experienced exacerbations of COPD during or following CO exposure, with one patient requiring hospitalization two months after exposure (initial symptoms first experienced 1-week post-exposure).
Hanada et al. (2003)	20 healthy males; 26 ± 1 years old	15 subjects exposed for 20 min (10 min rest, 5 min handgrip exercise, 2 min post-exercise ischemia, 3 min recovery) under the following four conditions: (1) normoxia (inspiratory O2 fraction 21.4%), (2) hypoxia (inspiratory O2 fraction 10.3%), (3) CO + normoxia, (4) CO + hyperoxia (inspiratory O2 fraction 95.9%). Inhaled CO administered to achieve ~20% COHb in venous blood. Each of the four conditions were separated by 20 min of rest. 5 subjects served as controls (four 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.
Kizakevich et al. (2000)	16 healthy non-smoking males; 18-29 years old	Subjects exposed on 4 separate days to increasing CO concentrations during either upper-body exercise (hand-crank) or lower-body exercise (treadmill). Targeted COHb levels were initially attained using short term (4-6 min) exposures to CO at concentrations between 1,000 and 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)	13 healthy non-smoking males; 18-38 years old	Subjects exposed to both 500 ppm CO and clean air for 1 h, with exposures separated by a 6-week period. Immediately following exposure, subjects were administered an intravenous bolus dose (2 ng/kg) of lipopolysaccharide (LPS).	The average COHb concentration was 7% following the 1 h CO exposure. 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)	12 healthy non-smoking males; 25 ± 2.9 years old	Exposures conducted on two separate occasions to both room air (6 min) and CO. Subjects were exposed to 3,000 ppm CO until COHb reached 6% (3-8 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)

Study	Subjects	Exposure	Findings
Ren et al. (2001)	12 healthy subjects; 11 nonsmokers; 9 males / 3 females; 20-32 years old	Each subject underwent four different 8 h experimental protocols: (1) isocapnic hypoxia (end-tidal PO2 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.
Resch et al. (2005)	15 healthy non-smoking males; 27 ± 4 years old	Subjects exposed to 500 ppm CO and synthetic air for 1 h at rest in a randomized crossover study design. Exposures were separated by a period of at least 1 week.	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).	10 healthy non-smoking males; 22-52 years old	Each subject was exposed to CO for 30-45 min to achieve a COHb level of 10%. Prior to and following exposure, subjects performed hypoxic and hyperoxic rebreathing tests. Four subjects were exposed to hypoxic conditions first, while six 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)	12 healthy male smokers; 27-47 years old	Exposures were conducted over 21 consecutive days under three different protocols, with each protocol lasting 7 days. In one protocol, subjects smoked 20 cigarettes per day, one every 45 min. In the other two protocols, every 45 min (20 times per day) subjects breathed either air or CO (~1200 ppm) from a 1 liter bag once per min for 10 min at a time. Subjects completed all three protocols, with six subjects exposed sequentially to CO, smoking, then air, and the other six 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 three exposures.

Annex E. Toxicological Studies

Table E-1.   Human and animal studies.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Acevedo and Ahmed (1998)	Human			HO-1 and HO-2 (mRNA and protein) were upregulated in pregnant myometrium when compared to non-pregnant myometrium. The HO activator hemin inhibited spontaneous and oxytocin-induced contractility of the myometrium. Progesterone induced HO-1 and HO-2 mRNA expression.
Achouh et al. (2008)	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)	Human			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 versus 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)	Human			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)	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)	Rat (Sprague Dawley)			The role of the HO/CO system in estrous cyclicity, pregnancy and lactation was evaluated using HO inhibitors and stubstrates. 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 (2003a)	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 (2003b)	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)	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 three other electron transport proteins.
Andresen et al. (2006)	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.
Antonelli et al. (2006)	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)	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.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Ashfaq et al. (2003)	Human plancenta			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 (1972)	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)	Human placenta			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)	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 hours, 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 + CO-exposed placental tissue had decreased apoptosis and decreased PARP (a protein marker of apoptosis) versus control H/R exposed cells. Secondary necrosis of the placental tissue post H/R was inhibited by CO treatment.
Bainbridge and Smith (2005)	Human placenta			The role of HO in the placenta and during pregnancy are 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)	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 $NO^\bullet$/CO/cGMP pathway.
Barber et al. (1999)	Human			HO and NOS did not maintain human uterine quiescence during pregnancy.
Barber et al. (2001)	Human placenta			Women who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant decreases in HO-2 versus healthy pregnancies.
Baum et al. (2000)	Human			End-tidal CO measurements in women with pregnancy-induced hypertension and pre-eclampsia were significantly lower than in normotensive pregnant women.
Bergeron et al. (1998)	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.
Bing et al. (1995)	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)	Human and Mouse			Nb had a high oxygen affinity similar to Mb, thus may increase the availabilty of O_2 to brain tissue.
Bye et al. (2008)	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)	Rat	GD0-GD20	75 or 150 ppm	At 5 months 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 with CO-exposed rats.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Carmines and Rajendran (2008)	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. (1995)	Rat (Wistar)		150 ppm	Sphingoipid homeostasis was disrupted in male offspring of prenatally exposed rats, without a disruption in motor function.
Carratu et al. (2000)	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, 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)	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)	Rat model of hypoxic pulmonary vascular remodeling Strain of rat not stated	3 weeks	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)	Rat (Sprague Dawley)			HO-1 production and HO concentration were shown to be regulated by estrogen in the rat uterus.
Chung et al. (2006)	Rat (Sprague Dawley) Male		3-6%	CO inactivation of Mb does not induce any change in the respiration rate, contractile function, or high-energy phosphate levels in perfused rat hearts.
Cronje et al. (2004)	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)
Cudmore et al. (2007)	Human placenta Human (HUVEC) Mouse (HO-1 deficient mouse on 129/SV x 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)	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)	Human (neonatal blood)			CO was lower at birth and 48-72 hours postpartum in infants born by elective C-section and higher in vaginally born infants.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
De Salvia et al. (1995)	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 months) and reacquisition (at 18 months) of conditioned avoidance behavior.
Denschlag et al. (2004)	Human			Genetic polymorphisms in human HO-1 are linked to idiopathic recurrent miscarriages.
Dewilde et al. (2001)				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.
Dubuis et al. (2002)	Rat (Wistar) Adult female 250 g	3 weeks	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.
Dubuis et al. (2005)	Rat (Wistar) Male	21 days	50 ppm	CO attenuated PAHT by activating BK_{Ca} channels in PA myocytes and reduced hemodynamic changes of PAHT.
Dubuis et al. (2003)	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.
Favory et al. (2006b)	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)	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 versus 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 versus air-exposed control dams.
Fechter et al. (1980)	Rat (Long Evans)	Continous CO exposure throughout pregnancy	150 ppm	CO-exposed animals had cardiomegaly at birth (wet heart weight) that dissipated by PND4.
Fechter and Annau (1980)	Rat	Continous 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)	Rat (Long Evans)	Continuous CO exposure throughout pregnancy or from GD0 to PND10	75, 150, or 300 ppm	The neostriatum of PND21 rat brains were 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).

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Garofolo et al. (2002)	Human infants Rat	Rat: PND2-PND5		Human infants who die from SIDS show decreased brainstem muscarinic receptor binding versus 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)	Rat (Wistar) Adult male Model of right ventricular hypertrophy secondary to chronic hypoxia	3 weeks of HH ± CO in final week Or 1 week 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 in-creased left ventricular shortening fraction (LVSF). CO alone led to a decrease in LVSF and the mitral E-to-A ratio, indicative of a 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-week 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)	Rat (Sprague Dawley)	2 h/day, 7 days/week by nose-only inhalation Males: 4 weeks prior to and during mating; and Females: 2 weeks 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)	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 incu-bating 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)	Rat (Wistar) Male and Pregnant female	From GD0-GD20 of pregnancy	75 or 150 ppm	This study showed that CO (75 and 150 ppm) exposed 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)	Rat (Wistar)	GD0-20	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.
Glabe et al. (1998)	Rat (Sprague Dawley) Male, Myocardium		P_{CO} = 0 - 107 Torr	Increased P_{CO} and increased COMb saturation did not alter high energy phosphate signals (ATP, phosphocreatine, P_i). MV_{O2} began to decline at 87.6% COMb and is likely not due to cytochrome c oxidase inhibition.
Grover et al. (2000)	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)	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)	Pig (Granulosa cells)			In this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular maturation.
Hendler and Baum (2004)	Human			End-tidal breath CO measurements in pregnant women with contractions (term and pre-term) were lower than those measurements in non-contracting women.
Hofmann and Brittain (1998)	Human			Partitioning of O_2 and CO in the human embryonic Hb is discussed.
Iheagwara et al. (2007)	Mouse (C57Bl6) 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)	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)	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)	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. Pre-treatment 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)	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• system in salt-sensitive rats treated with a high-salt diet.
Johnson et al. (2004)	Rat (Sprague Dawley) Male Deoxycorticosterone acetate (DOCA)-salt hypertension model WKY rats Spontaneously hypertensive rats (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 a 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)	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)	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)	Rat (Wistar)			Pregnancy-induced modulation of calcium mobilization and down-regulation of Rho-kinase expression contributed to attenuated vasopressin-induced contraction of the rat aorta.
Khan et al. (2006)	Nb overexpressing BDF × CD1 mice			Cerebral and myocardial infarcts were decreased in neuroglobin overexpressing mice, decreasing ischemic injury.
Kim et al. (2005)	Primary rat pulmonary artery smooth muscle cells Inbred LEW rat (Sprague Dawley) 200-250 g	24 h or pretreatment for 1-2 h followed by 24 h posttreatment	250 ppm	Exposure of cells in culture to 250 ppm CO for 24-h inhibited serum-stimulated cell proliferation, increased expression of p21[Waf1/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 p21[Waf1/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)	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 deter-mined 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)	Sheep (gravid and non-gravid 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)	Mouse	4 h	Diesel emissions: 350 $\mu g/m^3$	Diesel exhaust enhanced vasoconstriction in veins but not arteries. It was suggested that this is through the uncoupling of eNOS.
Kreiser et al. (2004)	Human			End tidal CO concentrations were lower in pregnant women with gestational hypertension and pre-eclampsia than normotensive women.
Lash et al. (2003)	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)	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 upregualtion post maternal LPS treatment.
Loennechen et al. (1999)	Rat (Sprague Dawley) Female 220-240g	1 week 1 week 100 ppm and 1 week 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 week exposure and by 43% and 12% in the left and right ventricle respectively during the 1 week exposure. Right ventricular to body weight ratio was increased by 18% and 16% in the 2 week and 1 week exposure groups respectively. COHb levels were 23% and 12% in the 2 week and 1 week exposure groups respectively.
Longo et al. (1999)	Rat (Sprague Dawley) Human			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.
Lopez et al. (2008)	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 show vacuolization of afferent terminals at the base of the cochlea. At PND3, group A shows decreased synapsin-1 staining of the efferent nerve terminals. At PND20, groups A and B show decreased neurofila-ment-IR (staining) in type I spiral ganglia neurons and afferent nerve fibers. At PND12 and PND20, group B shows increased HO-1 and SOD-1-IR in blood vessels of the stria vasularis; group A is similar to controls. From PND3-PND20, there is increased iNOS and increased nitrotyrosine-IR in blood vessels of the cochlea.
Lopez et al. (2003)	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 versus control. Expression of the calcium-mediated myosin ATPase in the organ of corti and spiral ganglion neurons was significantly de-creased in the 25 ppm CO exposure group versus controls.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Lund et al. (2007)	Mouse (ApoE$^{-/-}$) Male High fat diet	6 h/day, 7days/week, 7 weeks	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 and filtered 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)	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 ET$_A$ receptor. Treatment with BQ-123 also reduced aortic MMP-2/9 activity in aortas following gasoline exhaust exposure. The authors concluded that ET$_A$ receptor pathway is a key mediator of gasoline engine exhaust effects in the vasculature.
Lyall and Myatt (2002)	Human			Women with pre-eclampsia, produced term placenta with significant decreases in HO-2 versus women with healthy pregnancies.
Lyall et al. (2000)	Human (placentas from 8-19 weeks 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)	Rat (Long Evans)	Continous 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 and Westcott (1998)	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 this may be related to changes in the brainstem. COHb in maternal (8.53 ± 0.6% versus 0.25 ± 0.1%) and fetal blood (13.0 ± 0.4% versus 1.6 ± 0.1%) from CO-treated versus controls.
McLaughlin et al. (2001)	Human			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)	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)	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 versus normotensive pregnancies.
McLean et al. (2000)	Human placenta			HO activity was highest in the placenta near term.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Melin et al. (2002)	Rat (Dark Agouti) Male Model of right ventricle hypertrophy secondary to chronic hypoxia (HH 10 weeks)	10 weeks	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. Echo-cardiographic 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 $(+dP/dt_{LV})$, 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 $(+dP/dt_{RV}, -dP/dt_{RV})$ and right ventricular work (RVW). CO significantly enhanced the effects of HH on RVEDP and significantly diminished the effects of HH on dP/dt_{RV} 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)	Rat (Dark Agouti) Male and female Model of right ventricle hypertrophy secondary to chronic hypoxia (HH, 10 weeks) Half of the animals were exercise- trained to induce LV hypertrophy	10 weeks	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)	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)	Human Adult males aged 65-75. 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.
Naik and Walker (2003)	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)				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)	Mouse (CD-1)	GD7-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 versus 8% and 16% protein groups. Further, dietary restriction of both protein and zinc with CO-exposure to CO during gestation increased the incidence of pup mortality and malformations including gastroschisis. Zinc supplementation to protein deficient diet in CO-exposed mice decreased fetal mortality and malformation.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Newby et al. (2005)	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)	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)	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 tirgger apoptosis of pre-meiotic germ cells and modulate spermato-genesis under $CdCl_2$ dependent oxidative stress.
Patel et al. (2003)	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)	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.
Piantadosi (2002)				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)				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.
Piantadosi et al. (2006)	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 mitochon-dria from MPT. This effect was restored in the presence of a strong reductant. The authors conclude that CO causes mitochondrial pore stress independently of its hypoxic effects
Prigge and Hochrainer (1977)	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)				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)	Human Male		20% COHb	20% COHb did not influence O_2Mb binding indicated by unaltered deoxy-myoblobin 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)				Reviews the basic science of exogenous and endogenous CO including HO-1 regulation. It also reviews some therapeutic applications for CO.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Sartiani et al. (2004)	Rat (Wistar)	In utero inhalation exposure	150 ppm	At 4 weeks 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 I_{to} (transient outward current, K^+-mediated) and $I_{Ca,L}$ (L-type Ca^{2+} current), which largely control the rat APD, were significantly different from control animals after CO exposure at 4 weeks of age. All of these CO-dependent changes were no longer different from controls at 8 weeks of age, showing a delayed maturation.
Schwetz et al. (1979)	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 versus control. Increased birth weight in mice exposed to 7 h/day CO versus controls. No similar effects were seen in rabbits.
Singh et al. (1992)	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 have a synergistic effect on offspring survival and an additive effect on malformations.
Singh (2006)	Mouse (CD-1)	6 h/day during the first 2 weeks of pregnancy	65 or 125 ppm	Modulating dam protein intake during in utero CO exposure altered pup mortality.
Sitdikova et al. (2007)	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)	Human Primary human aortic 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 $p21^{Cip1}$ 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)	Rat (Wistar) Female 169 ± 4.5 g	20 h/day, x 5 days/week, x 72 weeks	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.
Stockard-Sullivan et al. (2003)	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) versus controls at PND22.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Suliman et al. (2007)	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	1-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 2-3 fold 24 h after exposure. CO activated gene expression of these proteins involved in cardiac mitochondrial biogenesis beginning at 2 h post exposure 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 post-exposure to 1,250 ppm CO for 1 h. Inhibition of p38 activation failed to inhibit the CO-mediated increase in cardiac mitochondrial biogenesis.\n\nIn 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.\n\nThe authors concluded that CO exposure increased mitochondrial ROS which promoted mitochondrial biogenesis in the heart.
Sun et al. (2001)	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)	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 months 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)	Human Myometrium tissue obtained from gravid [pre-term (25-34 weeks 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)	Rat (Dahl/Rapp salt-sensitive rats) Male		100 µM	A high salt diet for 1-4 weeks 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 weeks. 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 weeks 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)	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)	Rat (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 how NO• was measured (electrode versus 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)	Bovine pulmonary artery endothelial cells	30 min-4 h	10-100 ppm (11-110 nM)	1-h exposure to 111-110 nM CO led to a dose-dependent increase in NO$^\bullet$ 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 blacked 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 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 H_2O_2 or cellular redox activity. Exposure to 110 nM did not alter arginine transport or NOS activity. NO$^\bullet$ release from cells which had been pre-treated 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$^\bullet$. The authors concluded that endothelial cells release NO$^\bullet$ and NO$^\bullet$-derived oxidants in response to CO. A delayed cell death occurred following exposures to 22 nM and higher concentrations of CO.
Thom, et al. (1999b)	Rat (Wistar) Male 200-290 g Some rats 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 6-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$^\bullet$-derived oxidants.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1999a)	Rat (Wistar) Male 200-290 g	1 h	50-1,000 ppm	Leakage of albumin into lung parenchyma occurred 18 h, but not at earlier time points, after rats were exposed to 100 ppm CO for 1 h. 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)	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. (2001a)	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)	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)	Rat (Sprague Dawley) Males 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$^{\bullet}$, peaking at 100 nM and declining to undetectable responses at 10 µM. Sequential pulses of 100 nM resulted in a blunting of NO$^{\bullet}$ release with consecutive pulses, consistent with a depletion of intracellular NO$^{\bullet}$ stores. NO$^{\bullet}$ release was dependent on arginine concentrations and was inhibited by pretreatment with a NOS inhibitor. Perfusion with 100 nM CO blocked carbachol-dependent NO$^{\bullet}$ release from vessels. Rats were treated with a HO-1 inducer and renal resistance arteries were isolated 12 h later. Carbachol-induced NO$^{\bullet}$ 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$^{\bullet}$ from purified recombinant eNOS in solution. The authors concluded that low levels of CO may release NO$^{\bullet}$ and elicit vasorelaxation and modulate basal vascular tone while higher levels of CO may inhibit eNOS and NO$^{\bullet}$ generation.
Tolcos et al. (2000b)	Guinea pig	10 h/day over the last 60% of gestation	200 ppm	Fetal and 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. (2000a)	Guinea pig	10 h/day for the last 60% of gestation	200 ppm	Brains were collected at 1 and 8 weeks of age. These data showed that CO exposure in utero sensitized the brain to hyper-thermia at PND4 leading to generation of necrotic lesions in the brain and changes in neurotransmitter levels.
Tschugguel et al. (2001)	Human HUVEC			CO was generated by primary endothelial cells from human umbilical veins and uterine arteries after exogenous 17-ß estra-diol administration.
Vallone et al. (2004)	Mouse protein			The authors present the X-ray structure of CO-bound ferrous murine Nb. When CO binds, the heme group slides deeper into the protein crevice.
Vreman et al. (2000)	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 3x greater HO than the heart and 0.2x of the liver. HO activity in rat vasculature was 3x 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 vasulature (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)	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 3-fold increase in CO excretion reaching a maximaum 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)	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)	Rat Strain not stated	PND8-PND22	12.5, 25, or 50 ppm	Immunostaing 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.
Webber et al. (2005)	Rat Strain not stated	PND9-PND24	25 or 100 ppm	Neurofilament loss from the spiral gangilian 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).

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Wellenius et al. (2004)	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 µg/m³) 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. (2006b)	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 µg/m³) 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)	Human			HO localization in human endometrium and its changes in expression over the menstral cycle were explored in this study. HO-1 was constitutively expressed throughout the menstral cycle and HO-2 was greater in the secretory than the proliferative phase of the menstral 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.
Zamudio et al. (1995)	Human			Women living at high altitude had an increased risk of adverse pregnancy outcomes versus women living at lower altitudes.
Zenclussen et al. (2006)	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)	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.
Zhang et al. (2007)	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 post-LPS treatment. Pre-treatment of mice with the spin trap agent PBN or the TNFα inhibitor pentoxifylline prevented the LPS-dependent HO-1 upregulation. Thus ROS may mediate the LPS-dependent upregulation of HO-1.
Zhao et al. (2008)	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)	Rodent			Hippocampal LTP of brain sections is significantly affected by CO exposure with ZnPP IX, a HO inhibitor, blocking hippocampal LTP.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Zuckerbraun et al. (2007)	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

Abi Esber AL; El-Fadel M; Shihadeh A. (2007a). 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.

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

Abi Esber LA; El-Fadel M. (2008). In-vehicle CO ingression: Validation through field measurements and mass balance simulations. The Science of the total environment 394: 75-89.

Abram SR; Hodnett BL; Summers RL; Coleman TG; Hester RL. (2007). Quantitative Circulatory Physiology: an integrative mathematical model of human physiology for medical education. Advances in Physiology Education 31: 202.

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.

Achouh PE; Simonet S; Fabiani JN; Verbeuren TJ. (2008). Carbon monoxide induces relaxation of human internal thoracic and radial arterial grafts. Interactive CardioVascular and Thoracic Surgery 7: 959-962.

Adams KF; Koch G; Chatterjee B; Goldstein GM; O'Neil JJ; Bromberg PA; Sheps DS. (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.

Adams SM. (2003). Establishing causality between environmental stressors and effects on aquatic ecosystems. Hum Ecol Risk Assess 9: 17-35.

Adir Y; Merdler A; Ben Haim S; 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. Occupational and Environmental Medicine 56: 535-538.

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.

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 (Noisy-le-grand) 51: 447-451.

Akland GG, Hartwell, T.D., Johnson, T.R., Whitmore, R.W. (1985). Measuring human exposure to carbon monoxide in Washington, D.C. and Denver, Colorado during the winter of 1982-1983. Environmental Science and Technology 19: 911-918.

Alcantara RE; Xu C; Spiro TG; Guallar V. (2007). A quantum-chemical picture of hemoglobin affinity. Proceedings of the National Academy of Sciences 104: 18451-18455.

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.

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.

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.

Alexandreanu IC; Lawson DM. (2003a). Heme oxygenase in the rat anterior pituitary: immunohistochemical localization and possible role in gonadotropin and prolactin secretion. Exp Biol Med (Maywood) 228: 64-69.

Alexandreanu IC; Lawson DM. (2003b). Heme oxygenase in the rat ovary: immunohistochemical localization and possible role in steroidogenesis. Exp Biol Med (Maywood) 228: 59-63.

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.

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.

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

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.

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.

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.

Altshuller AP. (1991). Estimating product yields of carbon-containing products from the atmospheric photooxidation of ambient air alkenes. Journal of Atmospheric Chemistry 13: 131-154.

American Thoracic Society. (1985). 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.

American Thoracic Society. (2000). What constitutes an adverse health effect of air pollution? . American Journal of Respiratory and Critical Care Medicine 161: 665-673.

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.

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.

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. Occupational and Environmental Medicine 58: 504-510.

Andersson JA; Uddman R; Cardell LO. (2000). Carbon monoxide is endogenously produced in the human nose and paranasal sinuses. J Allergy Clin Immunol 105: 269-273.

Andreae MO. (1991). Biomass burning: Its history, use, and distribution and its impact on environmental quality and global climate. Global Biomass Burning: Atmospheric, Climatic, and Biospheric Implications (JS Levine, Ed.). In Ecological studies, Voll. 84. Analysis and synthesis. The MIT Press, Cambridge.

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: H223-230.

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: 568-576.

Appel KW; Bhave PV; Gilliland AB; Sarwar G; Roselle SJ. (2008). Evaluation of the community multiscale air quality (CMAQ) model version 4.5: Sensitivities impacting model performance; Part II—particulate matter. Atmos Environ 42: 6057-6066.

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: H2055-2059.

Ashfaq M; Janjua MZ; Nawaz M. (2003). Effects of maternal smoking on placental morphology. J Ayub Med Coll Abbottabad 15: 12-15.

Astrup P; Olsen HM; Trolle D; Kjeldsen K. (1972). Effect of moderate carbon-monoxide exposure on fetal development. Lancet 2: 1220-1222.

Atkinson RW; Anderson HR; Strachan DP; Bland JM; Bremner SA; Ponce de Leon A. (1999). Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J 13: 257-265.

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.

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. Journal of Thrombosis and Haemostasis 5: 252-260.

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.

Bainbridge SA; Smith GN. (2005). HO in pregnancy. Free Radic Biol Med 38: 979-988.

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.

Bakwin PS; Tans PP; Novelli PC. (1994). Carbon monoxide budget in the Northern Hemisphere. Geophys Res Lett 21.

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.

Baldauf RW, N. Watkins, D. Heist, C. Bailey, P. Rowley, R. Shores. 2009. Near-Road Air Quality Monitoring: Factors Affecting Network Design and Interpretation of Data, J. of Air Quality, Atmosphere, & Health (in press). (In press). Near-road air quality monitoring: Factors affecting network Design and Interpretation of data. J of Air Quality, Atmosphere, & Health.

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.

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 admissions association in Spain: results within the EMECAS project. J Epidemiol Community Health 60: 328-336.

Bamberger AM; 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 alpha(2) subunit. J Clin Endocrinol Metab 86: 909-912.

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.

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: 1158-1168.

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.

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.

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.

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.

Beard RR; Wertheim GA. (1967). Behavioral impairment associated with small doses of carbon monoxide. In American Journal of Public Health (Vol. 57, pp. 2012).

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 70: 261-265.

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.

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

Bell ML; Ebisu K; Belanger K. (2007). Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ Health Perspect 115: 1118-1124.

Bell ML; Levy JK; Lin Z. (2008). The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. Occupational and Environmental Medicine 65: 104-111.

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.

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.

Benignus VA. (1993). Importance of experimenter-blind procedure in neurotoxicology. Neurotoxicol Teratol 15: 45-49.

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.

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 Methods 16: 27-36.

Bergamaschi P; Hein R; Heimann M; Crutzen PJ. (2000). Inverse modeling of the global CO cycle 1. Inversion of CO mixing ratios. Journal of Geophysical Research 105: 1909-1927.

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: 1149-1158.

Bergeron M; Ferriero DM; Sharp FR. (1998). Developmental expression of heme oxygenase-1 (HSP32) in rat brain: an immunocytochemical study. Brain Res Dev Brain Res 105: 181-194.

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.

Berk PD; Blaschke TF; Scharschmidt BF; Waggoner JG; Berlin NI. (1976). A new approach to quantitation of the various sources of bilrubin in man. J Lab Clin Med 87: 767-780.

Berkowitz GS; Papiernik E. (1993). Epidemiology of Preterm Birth. Epidemiol Rev 15: 414-443.

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.

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.

Bogo H; Gómez DR; Reich SL; Negri RM; San Román E. (2001). Traffic pollution in a downtown site of Buenos Aires City. Atmos Environ 35: 1717-1727.

Bol KA; Collins JS; Kirby RS. (2006). Survival of infants with neural tube defects in the presence of folic acid fortification. Pediatrics 117: 803-813.

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.

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.

Botter DA; Jorgensen B; Peres AA. (2002). A longitudinal study of mortality and air pollution for Sao Paulo, Brazil. J Expo Anal Environ Epidemiol 12: 335-343.

Botto LD; Correa A; Erickson JD. (2001). Racial and temporal variations in the prevalence of heart defects. Pediatrics 107: E32.

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 37.

Braga AL; Saldiva PH; Pereira LA; Menezes JJ; Conceicao GM; 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.

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.

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. Occupational and Environmental Medicine 56: 237-244.

Brian JE, Jr.; Heistad DD; Faraci FM. (1994). Effect of carbon monoxide on rabbit cerebral arteries. Stroke 25: 639-643; discussion 643-634.

Brown SD; Piantadosi CA. (1992). Recovery of energy metabolism in rat brain after carbon monoxide hypoxia. J Clin Invest 89: 666-672.

Bruce EN; Bruce MC. (2003). A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. J Appl Physiol 95: 1235-1247.

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.

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.

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.

Brune B; Ullrich V. (1987). Inhibition of platelet aggregation by carbon monoxide is mediated by activation of guanylate cyclase. Mol Pharmacol 32: 497-504.

Buck S; Dodds W; Fisher J; Hart D; Parker A; Stevenson J; Watson V; Welch E. (2000). Nutrient criteria technical guidance manual, rivers and streams: US Environmental Protection Agency, Office of Water. EPA-822-B-00-002,

Burke JM; Zufall MJ; Ozkaynak H. (2001). A population exposure model for particulate matter: case study results for PM (2.5) in Philadelphia, PA. J Expo Anal Environ Epidemiol 11: 470-489.

Burmester T; Weich B; Reinhardt S; Hankeln T. (2000). A vertebrate globin expressed in the brain. Nature 407: 520-523.

Burnett RT; Smith-Doiron M; Stieb D; Cakmak S; Brook JR. (1999). Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Archives of Environmental Health 54: 130-139.

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.

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. American Journal of Epidemiology 153: 444-452.

Burnett RT; Goldberg MS. (2003). Size-fractionated particulate mass and daily mortality in eight Canadian cities. Revised Analyses of Time-Series Studies of Air Pollution and Health Special Report Boston: Health Effects Institute: 85–90.

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. Archives of Environmental Health 59: 228-236.

Bye A; Sorhaug S; Ceci M; Hoydal MA; Stolen T; Heinrich G; Tjonna AE; Najjar SM; Nilsen OG; Catalucci D; Grimaldi S; Contu R; Steinshamn S; Condorelli G; Smith GL; Ellingsen O; Waldum H; Wisloff U. (2008). Carbon monoxide levels experienced by heavy smokers impair aerobic capacity and cardiac contractility and induce pathological hypertrophy. Inhalation Toxicology 20: 635-646.

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.

Cakmak S; Dales RE; Judek S. (2006a). Respiratory Health Effects of Air Pollution Gases: Modification by Education and Income. Archives of Environmental Health 61: 5-10.

Cakmak S; Dales RE; Judek S. (2006b). Do gender, education, and income modify the effect of air pollution gases on cardiac disease? J Occup Environ Med 48: 89-94.

Cakmak S; Dales RE; Vidal CB. (2007). Air pollution and mortality in Chile: susceptibility among the elderly. Environ Health Perspect 115: 524-527.

Cardell LO; 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.

Carmines EL; 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: 383-391.

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.

Carratu MR; Cagiano R; De Salvia MA; Trabace L; Cuomo V. (1995). Developmental neurotoxicity of carbon monoxide. Arch Toxicol Suppl 17: 295-301.

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.

Carratù 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.

Carraway MS; Ghio AJ; Carter JD; Piantadosi CA. (2000). Expression of heme oxygenase-1 in the lung in chronic hypoxia. American journal of physiology Lung cellular and molecular physiology 278: L806.

Carraway MS; Ghio AJ; Suliman HB; Carter JD; Whorton AR; Piantadosi CA. (2002). Carbon monoxide promotes hypoxic pulmonary vascular remodeling. American Journal of Physiology- Lung Cellular and Molecular Physiology 282: 693-702.

Carter WPL. (1998). Updated maximum incremental reactivity scale for regulatory applications. Preliminary Report to California Air Resources BoardContract 95308.

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.

Cavallin-Stahl E; Mercke C; Lundh B. (1976a). Erythropoiesis and Carbon Monoxide Production in Hodgkin's Disease. Br J Haematol 32: 167-176.

Cavallin-Stahl E; Mercke C; Lundh B. (1976b). Carbon monoxide production in patients with breast carcinoma. Br J Haematol 32: 177-182.

CDC. (2004). The health consequences of smoking: a report of the Surgeon General. U.S. Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available from: http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/chapters.htm, Atlanta, GA. Available from: http://www.cdc.gov/tobacco/sgr/sgr_2004/index.htm.

Cella M; Farina MG; Keller Sarmiento MI; 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.

Centers for Disease Control and Prevention. (1998). Trends in infant mortality attributable to birth defects--United States, 1980-1995. MMWR Morb Mortal Wkly Rep 47: 773-778.

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.

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.

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

Chan CC; Chuang KJ; Su TC; Lin LY. (2005). Association between nitrogen dioxide and heart rate variability in a susceptible population. Eur J Cardiovasc Prev Rehabil 12: 580-586.

Chan CC; Chuang KJ; Chien LC; Chen WJ; Chang WT. (2006). Urban air pollution and emergency admissions for cerebrovascular diseases in Taipei, Taiwan. Eur Heart J 27: 1238-1244.

Chang CC; Tsai SS; Ho SC; Yang CY. (2005). Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. Environ Res 98: 114-119.

Chang CH; Meroney RN. (2003). Concentration and flow distributions in urban street canyons: wind tunnel and computational data. Journal of Wind Engineering & Industrial Aerodynamics 91: 1141-1154.

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

Chang LT; 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 O-3, PM2.5, and CO. J Air Waste Manage Assoc 51: 1414-1422.

Chen GD; Kong J; Reinhard K; Fechter LD. (2001). NMDA receptor blockage protects against permanent noise-induced hearing loss but not its potentiation by carbon monoxide. Hearing Res 154: 108-115.

Chen H; Namdeo A; Bell M. (2008). Classification of road traffic and roadside pollution concentrations for assessment of personal exposure. Environmental Modelling & Software 23: 282-287.

Chen L; Jennison BL; Yang W; Omaye ST. (2000). Elementary school absenteeism and air pollution. Inhalation Toxicology 12: 997-1016.

Chen L; Yang W; Jennison BL; Goodrich A; Omaye ST. (2002). Air pollution and birth weight in northern Nevada, 1991-1999. Inhalation Toxicology 14: 141-157.

Chen PC; Lai YM; Chan CC; Hwang JS; Yang CY; Wang JD. (1999). Short-term effect of ozone on the pulmonary function of children in primary school. Environ Health Perspect 107: 921-925.

Cheng MF; Tsai SS; Wu TN; Chen PS; Yang CY. (2007). Air pollution and hospital admissions for pneumonia in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A 70: 2021-2026.

Chevalier RB; Krumholz RA; Ross JC. (1966). Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. Journal of the American Medical Association 198: 1061-1064.

Chin BY; Jiang G; Wegiel B; Wang HJ; MacDonald T; Zhang XC; Gallo D; Cszimadia E; Bach FH; Lee PJ. (2007). Hypoxia-inducible factor 1alpha stabilization by carbon monoxide results in cytoprotective preconditioning. Proceedings of the National Academy of Sciences 104: 5109.

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.

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 Manage Assoc 50: 1481-1500.

Chung Y; Huang SJ; Glabe A; Jue T. (2006). Implication of CO inactivation on myoglobin function. American Journal of Physiology- Lung Cellular and Molecular Physiology 290: C1616-1624.

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 Manage Assoc 50: 1287-1298.

Clewell HJ; Crump KS. (2005). Quantitative Estimates of Risk for Noncancer Endpoints. An International Journal 25: 285-289.

Coburn RF; Williams WJ; Forster RE. (1964). Effect of Erythrocyte Destruction on Carbon Monoxide Production in Man. J Clin Invest 43: 1098-1103.

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.

Coburn RF; Williams WJ; Kahn SB. (1966). Endogenous carbon monoxide production in patients with hemolytic anemia. J Clin Invest 45: 460-468.

Coburn RF. (1967). Endogenous carbon monoxide production and body CO stores. Acta Med Scand Suppl 472: 269-282.

Coburn RF. (1970a). The carbon monoxide body stores. Ann N Y Acad Sci 174: 11-22.

Coburn RF. (1970b). Enhancement by phenobarbital and diphenylhydantoin of carbon monoxide production in normal man. N Engl J Med 283: 512-515.

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. Circul Res 62: 471-477.

Collier TK. (2003). Forensic Ecotoxicology: Establishing Causality between Contaminants and Biological Effects in Field Studies. Hum Ecol Risk Assess 9: 259 - 266.

Conceicao GM; Miraglia SG; Kishi HS; Saldiva PH; Singer JM. (2001). Air pollution and child mortality: a time-series study in Sao Paulo, Brazil. Environ Health Perspect 109 Suppl 3: 347-350.

Conny JM. (1998). The isotopic characterization of carbon monoxide in the troposphere. Atmos Environ 32: 2669-2683.

Conrad R; Seiler W. (1985). Influence of temperature, moisture, and organic carbon on the flux of H 2 and CO between soil and atmosphere: Field studies in subtropical regions. Journal of Geophysical Research 90: 5699-5709.

Cronje FJ; Carraway MS; Freiberger JJ; Suliman HB; Piantadosi CA. (2004). Carbon monoxide actuates O(2)-limited heme degradation in the rat brain. Free Radic Biol Med 37: 1802-1812.

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

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.

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 115: 1789-1797.

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.

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.

Dales R. (2004). Ambient carbon monoxide may influence heart rate variability in subjects with coronary artery disease. J Occup Environ Med 46: 1217-1221.

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.

Davies DM; Smith DJ. (1980). Electrocardiographic changes in healthy men during continuous low-level carbon monoxide exposure. Environ Res 21: 197-206.

Davies RF; Topping DL; Turner DM. (1976). The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. Atherosclerosis 24: 527-536.

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. American Journal of Epidemiology 157: 613-623.

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 196-187.

De Leon SF; Thurston GD; Ito K. (2003). Contribution of respiratory disease to nonrespiratory mortality associations with air pollution. American Journal of Respiratory and Critical Care Medicine 167: 1117-1123.

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 (Berl) 122: 66-71.

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 Pharmacotherapy (pp. 3029): McGraw-Hill.

Delfino RJ; Gong H, Jr.; 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.

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.

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 Human Reprod 10: 211-214.

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.

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.

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

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.

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.

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. American Journal of Epidemiology 156: 193-203.

Dominici F; Sheppard L; Clyde M. (2003a). Health Effects of Air Pollution: A Statistical Review. International Statistical Review 71: 243-276.

Dominici F; McDermott A; Daniels M; Zeger SL; Samet JM. (2003b). Mortality among residents of 90 cities. Revised Analyses of Time-Series Studies of Air Pollution and Health Special Report Boston, MA: Health Effects Institute: 9–24.

Dominici F; Zanobetti A; Zeger SL; Schwartz J; Samet JM. (2005a). The National Morbidity, Mortality, and Air Pollution Study Part IV: Hierarchical Bivariate Time-Series Models-A Combined Analysis of PM~ 1~ 0 Effects on Hospitalization and Mortality. Health Effects Institute,

Dominici F; McDermott A; Daniels M; Zeger SL; Samet JM. (2005b). Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. J Toxicol Environ Health A 68: 1071-1092.

Douglas CG; Haldane JS; Haldane JBS. (1912). The laws of combination of haemoglobin with carbon monoxide and oxygen. The Journal of Physiology 44: 275.

Drinkwater BL; Raven PB; Horvath SM; Gliner JA; Ruhling RO; Bolduan NW; Taguchi S. (1974). Air pollution, exercise, and heat stress. Archives of Environmental Health 28: 177-181.

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. American Journal of Physiology- Lung Cellular and Molecular Physiology 283: L120-129.

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.

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.

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

Dutton SJ; Hannigan MP; Miller SL. (2001). Indoor pollutant levels from the use of unvented natural gas fireplaces in Boulder, Colorado. J Air Waste Manage Assoc 51: 1654-1661.

Ekblom B; Huot R. (1972). Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol Scand 86: 474-482.

Engel LA. (1983). Gas mixing within the acinus of the lung. J Appl Physiol 54: 609-618.

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.

Enzi G; Bevilacqua M; Crepaldi G. (1976). Disturbances in pulmonary gaseous exchange in primary hyperlipoproteinemias. Bull Eur Physiopathol Respir 12: 433-442.

Ernst A; Zibrak JD. (1998). Carbon Monoxide Poisoning. New Engl J Med 339: 1603-1608.

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: 607-611.

Fairley D. (1999). Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ Health Perspect 107: 637-641.

Farhat SC; Paulo RL; Shimoda TM; Conceicao GM; Lin CA; Braga AL; Warth MP; Saldiva PH. (2005). Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. Braz J Med Biol Res 38: 227-235.

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: G1184-1189.

Favory R; Lancel S; Marechal X; Tissier S; Neviere R. (2006a). Cardiovascular protective role for activated protein C during endotoxemia in rats. Intensive Care Med 32: 899-905.

Favory R; Lancel S; Tissier S; Mathieu D; Decoster B; Neviere R. (2006b). Myocardial dysfunction and potential cardiac hypoxia in rats induced by carbon monoxide inhalation. American Journal of Respiratory and Critical Care Medicine 174: 320-325.

Fechter LD; Annau Z. (1977). Toxicity of mild prenatal carbon monoxide exposure. Science 197: 680-682.

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.

Fechter LD; Annau Z. (1980). Prenatal carbon monoxide exposure alters behavioral development. Neurobehav Toxicol 2: 7-11.

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.

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.

Fechter LD; Chen G; Rao D. (2002). Chemical asphyxiants and noise. Noise Health 4: 49.

Fenn WO. (1970). The burning of CO in tissues. Ann N Y Acad Sci 174: 64-71.

Finlayson-Pitts BJ; Pitts Jr JN. (2000). Chemistry of the Upper and Lower Atmosphere Theory, Experiments, and Applications. San Diego: Academic Press.

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? European Respiratory Journal 21: 34S-38S.

Fischer PH; Steerenberg PA; Snelder JD; van Loveren H; van Amsterdam JG. (2002). Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. Int Arch Occup Environ Health 75: 348-353.

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.

Fishman J; Bowman KW; Burrows JP; Richter A; Chance KV; Edwards DP; Martin RV; Morris GA; Pierce RB; Ziemke JR. (2008). Remote Sensing of Tropospheric Pollution from Space. Bulletin of the American Meteorological Society 89: 805-821.

Flachsbart PG. Models of exposure to carbon monoxide inside a vehicle on a Honolulu highway. Journal of Exposure Analysis and Environmental Epidemiology 9: 245.

Fodor GG; Winneke G. (1972). Effect of low CO concentrations on resistance to monotony and on psychomotor capacity. Staub Reinhaltung Der Luft 32: 46-54.

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. American Journal of Respiratory and Critical Care Medicine 172: 1549-1555.

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.

Forster RE. (1966). Diffusion of gases in the lungs. Physiologist 9: 110-122.

Fox GA. (1991). Practical causal inference for ecoepidemiologists. J Toxicol Environ Health 33: 359-373.

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.

Fung KY; Khan S; Krewski D; Chen Y. (2006). Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. Inhalation Toxicology 18: 1005-1011.

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.

Garofolo MC; Seidler FJ; Auman JT; Slotkin TA. (2002). ß-Adrenergic modulation of muscarinic cholinergic receptor expression and function in developing heart. American Journal of Physiology- Regulatory, Integrative and Comparative Physiology 282: 1356-1363.

Gautier M; Antier D; Bonnet P; Net JLL; 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.

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.

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

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

Gerritsen J; Carlson RE; Dycus DL; Faulkner C; Gibson GR. (1998). Lake and reservoir bioassessment and biocriteria: Technical guidance document. EPA 841-B-98-007. US Environmental Protection Agency, Office of Water, Washington, DC. http://www.epa.gov/owow/monitoring/tech/lakes.html,

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.

Gibson QH; Roughton FJ. (1955). The kinetics of dissociation of the first oxygen molecule from fully saturated oxyhaemoglobin in sheep blood solutions. Proc R Soc Lond B Biol Sci 143: 310-334.

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.

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. American Journal of Epidemiology 162: 238-252.

Gilliam RC; Huber AH; Raman S; Neogi D. (2005). Metropolitan-Scale Transport and Dispersion of Materiel Released from the New York World Trade Center Following September 11, 2001—Part II: The CALPUFF Plume Model. Pure and Applied Geophysics 162: 2005-2028.

Gilliland F; Avol PK; Kinney PL; 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: 1447-1454.

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. Pharmacol Toxicol 73: 274-278.

Giustino A; Carratu MR; Siro BG; 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.

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.

Glabe A; Chung Y; Xu D; Jue T. (1998). Carbon monoxide inhibition of regulatory pathways in myocardium. Am J Physiol 274: H2143-2151.

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. Circulation 101: 1267-1273.

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.

Goldberg MS; Burnett RT; Bailar JC, 3rd; Tamblyn R; Ernst P; Flegel K; Brook J; Bonvalot Y; Singh R; Valois MF; Vincent R. (2001). Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ Health Perspect 109 Suppl 4: 487-494.

Goldberg MS; Burnett RT; Valois MF; Flegel K; Bailar JC, 3rd; 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.

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. Environmental Research 100: 255.

Goldstein AH; Galbally IE. (2007). Known and unexplored organic constituents in the earth's atmosphere. Environmental Science and Technology 41: 1514–1521.

Gomez-Perales JE; Colvile RN; Nieuwenhuijsen MJ; Fernández-Bremauntz A; Gutiérrez-Avedoy VJ; Páramo-Figueroa VH; Blanco-Jiménez S; Bueno-López E; Mandujano F; Bernabe-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.

Gomez-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. (2007). Bus, minibus, metro inter-comparison of commuters' exposure to air pollution in Mexico City. Atmos Environ 41: 890-901.

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. American Journal of Respiratory and Critical Care Medicine 169: 816-821.

Gouveia N; Fletcher T. (2000a). Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occupational and Environmental Medicine 57: 477-483.

Gouveia N; Fletcher T. (2000b). Time series analysis of air pollution and mortality: effects by cause, age and socioeconomic status. J Epidemiol Community Health 54: 750-755.

Gouveia N; Bremner SA; Novaes HM. (2004). Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health 58: 11-17.

Grosjean D; Fung K. (1984). Hydrocarbons and carbonyl in Los Angeles air. J Air Pollut Control Assoc 34.

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. American Journal of Physiology- Lung Cellular and Molecular Physiology 278: L779-784.

Gryparis A; Forsberg B; Katsouyanni K; Analitis A; Touloumi G; Schwartz J; Samoli E; Medina S; Anderson HR; Niciu EM. (2004). Acute Effects of Ozone on Mortality from the" Air Pollution and Health: A European Approach" Project. American Journal of Respiratory and Critical Care Medicine 170: 1080.

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

Guo YL; Lin YC; Sung FC; Huang SL; Ko YC; Lai JS; Su HJ; Shaw CK; Lin RS; Dockery DW. (1999). Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in taiwan. Environ Health Perspect 107: 1001-1006.

Guyatt AR; Holmes MA; Cumming G. (1981). Can carbon monoxide be absorbed from the upper respiratory tract in man? Eur J Respir Dis 62: 383-390.

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.

Ha EH; Hong YC; Lee BE; Woo BH; Schwartz J; Christiani DC. (2001). Is air pollution a risk factor for low birth weight in Seoul? Epidemiology 12: 643-648.

Ha EH; Lee JT; Kim H; Hong YC; Lee BE; Park HS; Christiani DC. (2003). Infant susceptibility of mortality to air pollution in Seoul, South Korea. Pediatrics 111: 284-290.

Haab P. (1990). The effect of carbon monoxide on respiration. Experientia 46: 1202-1206.

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.

Hajat S; Anderson HR; Atkinson RW; Haines A. (2002). Effects of air pollution on general practitioner consultations for upper respiratory diseases in London. Occupational and Environmental Medicine 59: 294-299.

Haldane J. (1898). Some improved methods of gas analysis. The Journal of Physiology 22: 465.

Hampson NB. (2007). Carboxyhemoglobin elevation due to hemolytic anemia. J Emerg Med 33: 17-19.

Hanada A; Sander M; Gonzalez-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.

Hanel B; Teunissen I; Rabol A; Warberg J; Secher NH. (1997). Restricted postexercise pulmonary diffusion capacity and central blood volume depletion (Vol. 83, pp. 11-17): Am Physiological Soc.

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 and Built Environment 15: 147-153.

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.

Harada T; Koi H; Kubota T; Aso T. (2004). Haem oxygenase augments porcine granulosa cell apoptosis in vitro. J Endocrinol 181: 191-205.

Harley RA; McKeen SA; Pearson J; Rodgers MO; Lonneman WA. (2001). Analysis of motor vehicle emissions during the Nashville/Middle Tennessee Ozone Study. Journal of Geophysical Research 106: 3559–3567.

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. Environmental Science and Technology 39: 5356-5362.

Hausberg M; Somers VK. (1997). Neural circulatory responses to carbon monoxide in healthy humans. Hypertension 29: 1114-1118.

Hegewald MJ; Crapo RO. (2007). Socioeconomic status and lung function. Chest 132: 1608-1614.

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.

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. Occupational and Environmental Medicine 64: 439-445.

Hering SV. (2007). Using Regional Data and Building Leakage to Assess Indoor Concentrations of Particles of Outdoor Origin. Aerosol Science and Technology 41: 639-654.

Hermans RH; McGivern RF; Chen W; Longo LD. (1993). Altered adult sexual behavior in the male rat following chronic prenatal hypoxia. Neurotoxicol Teratol 15: 353-363.

Hill AB. (1965). The Environment and Disease: Association or Causation? Proc R Soc Med 58: 295-300.

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: H311-323.

Hinwood AL; De Klerk N; Rodriguez C; Jacoby P; Runnion T; Rye P; Landau L; Murray F; Feldwick M; Spickett JCEH. (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.

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.

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.

Hoek G; Brunekreef B; Fischer P; van Wijnen J. (2001). The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12: 355-357.

Hoek G. (2003). Daily mortality and air pollution in The Netherlands. In Revised analyses of time-series studies of air pollution and health. Health Effects Institute, Boston, MA.

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

Hofmann OM; Brittain T. (1998). Partitioning of oxygen and carbon monoxide in the three human embryonic hemoglobins. Hemoglobin 22: 313-319.

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.

Holland RA. (1970). Reaction rates of carbon monoxide and hemoglobin. Ann N Y Acad Sci 174: 154-171.

Hong YC; Leem JH; Ha EH. (1999a). Air pollution and daily mortality in Inchon, Korea. J Korean Med Sci 14: 239-244.

Hong YC; Leem JH; Ha EH; Christiani DC. (1999b). PM(10) exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. Environ Health Perspect 107: 873-878.

Hong YC; Lee JT; Kim H; Ha EH; Schwartz J; Christiani DC. (2002a). Effects of air pollutants on acute stroke mortality. Environ Health Perspect 110: 187-191.

Hong YC; Lee JT; Kim H; Kwon HJ. (2002b). Air pollution: a new risk factor in ischemic stroke mortality. Stroke 33: 2165-2169.

Horvath SM; Dahms TE; O'Hanlon JF. (1971). Carbon monoxide and human vigilance. A deleterious effect of present urban concentrations. Archives of Environmental Health 23: 343-347.

Horvath SM; Raven PB; Dahms TE; Gray DJ. (1975). Maximal aerobic capacity at different levels of carboxyhemoglobin. J Appl Physiol 38: 300-303.

Horvath SM; Bedi JF; Wagner JA; Agnew J. (1988). Maximal aerobic capacity at several ambient concentrations of CO at several altitudes. J Appl Physiol 65: 2696-2708.

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.

Hsia CC. (2002). Recruitment of lung diffusing capacity: update of concept and application. Chest 122: 1774-1783.

Huikuri HV; Jokinen V; Syvanne M; Nieminen MS; Airaksinen KE; Ikaheimo MJ; Koistinen JM; Kauma H; Kesaniemi AY; Majahalme S; Niemela KO; Frick MH. (1999). Heart rate variability and progression of coronary atherosclerosis. Atertio Thromb Vasc Biol 19: 1979-1985.

Hutcheon JA; Platt RW. (2008). The missing data problem in birth weight percentiles and thresholds for "Small-for-Gestational-Age". American Journal of Epidemiology 167: 786-792.

Huynh M; Woodruff TJ; Parker JD; Schoendorf KC. (2006). Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol 20: 454-461.

Hwang B; Jaakkola JK. (2008). Ozone and Other Air Pollutants and the Risk of Oral Clefts Environ Health Perspect 116: 1411–1415

Hwang BF; Lee YL; Lin YC; Jaakkola JJ; Guo YL. (2005). Traffic related air pollution as a determinant of asthma among Taiwanese school children. Thorax 60: 467-473.

Hwang BF; Jaakkola JJ; Lee YL; Lin YC; Guo YL. (2006). Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res 7: 23.

Hwang JS; Chan CC. (2002). Effects of air pollution on daily clinic visits for lower respiratory tract illness. American Journal of Epidemiology 155: 1-10.

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

Ibald-Mulli A; Stieber J; Wichmann HE; Koenig W; Peters A. (2001). Effects of air pollution on blood pressure: a population-based approach. Am J Public Health 91: 571-577.

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.

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.

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. Circul Res 89: 55-62.

Inman RE; Ingersoll RB; Levy EA. (1971). Soil: A Natural Sink for Carbon Monoxide. Science 172: 1229-1231.

IOM (2008). Improving the Presumptive Disability Decision-Making Process for Veterans. In Samet James M, Bodurow CC (Eds.),

IPCC. (2001). Climate Change 2001: The Scientific Basis. Cambridge Univ. Press, Cambridge, UK.

IPCC. (2007). Climate Change 2007: The Physical Science Basis. Cambridge Univ. Press, Cambridge, UK.

Ischiropoulos H; Beers MF; Ohnishi ST; Fisher D; Garner SE; Thom SR. (1996). Nitric oxide production and perivascular nitration in brain after carbon monoxide poisoning in the rat. J Clin Invest 97: 2260-2267.

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: S45-60.

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.

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.

Jeffries HE. (1995). Photochemical air pollution. In Singh HB (Ed.), Composition, chemistry, and climate of the atmosphere (pp. 308-348). New York, NY: Van Nostrand Reinhold.

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 66: 1735-1777.

Jerrett M; Arain A; Kanaroglou P; Beckerman B; Potoglou D; Sahsuvaroglu T; Morrison J; Giovis C. (2004). A review and evaluation of intraurban air pollution exposure models. Journal of Exposure Science and Environmental Epidemiology 15: 185-204.

Johnson FK; Johnson RA. (2003). Carbon monoxide promotes endothelium-dependent constriction of isolated gracilis muscle arterioles. American Journal of Physiology- Regulatory, Integrative and Comparative Physiology 285: 536-541.

Johnson FK; Durante W; Peyton KJ; Johnson RA. (2003). Heme oxygenase inhibitor restores arteriolar nitric oxide function in Dahl rats. Hypertension 41: 149-155.

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.

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. American Journal of Physiology- Regulatory, Integrative and Comparative Physiology 290: 601-608.

Johnson T. (1984). A Study of Personal Exposure to Carbon Monoxide in Denver, Colorado. Research Triangle Park, NC: US Environmental Protection Agency, Environmental Monitoring Systems Laboratory; report no. EPA-600/4-84-014,

Joumard R; Chiron M; Vidon R; Maurin M; Rouzioux JM. (1981). Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. Environ Health Perspect 41: 277-289.

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

Kanten WE; Penney DG; Francisco K; Thill JE. (1983). Hemodynamic responses to acute carboxyhemoglobinemia in the rat. Am J Physiol 244: H320-327.

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.

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. American Journal of Epidemiology 165: 553-560.

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

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: 220-227.

Katoue MG; Khan I; Oriowo MA. (2006). Pregnancy-induced modulation of calcium mobilization and down-regulation of Rho-kinase expression contribute to attenuated vasopressin-induced contraction of the rat aorta. Vascul Pharmacol 44: 170-176.

Katsouyanni K; Touloumi G; Samoli E; Gryparis A; Le Tertre A; Monopolis Y; Rossi G; Zmirou D; Ballester F; Boumghar A. (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.

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.

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.

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.

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.

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

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. Proceedings of the National Academy of Sciences 103: 17944-17948.

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. Journal of Exposure Science and Environmental Epidemiology 16: 172-183.

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. Proceedings of the National Academy of Sciences 102: 11319-11324.

Kim HS; Loughran PA; Rao J; Billiar TR; Zuckerbraun BS. (2008). Carbon monoxide activates NF-kappaB via ROS generation and Akt pathways to protect against cell death of hepatocytes. American Journal of Physiology Gastrointestinal and Liver Physiology 295: G146-G152.

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.

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

Kingdom JCP; Kaufmann P. (1997). Oxygen and placental villous development: Origins of fetal hypoxia. Placenta 18: 613-621.

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.

Kinobe RT; Vlahakis JZ; Soong JM; Szarek WA; Brien JF; Longo LD; 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.

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.

Klasner AE; Smith SR; Thompson MW; Scalzo AJ. (1998). Carbon monoxide mass exposure in a pediatric population. Acad Emerg Med 5: 992-996.

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 Suppl 103: 26-38.

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. Archives of Environmental Health 44: 361-369.

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. Archives of Environmental Health 53: 388-397.

Klemm RJ; Lipfert FW; Wyzga RE; Gust C. (2004). Daily mortality and air pollution in Atlanta: two years of data from ARIES. Inhalation Toxicology 16 Suppl 1: 131-141.

Klepeis NE; Nelson WC; Ott WR; Robinson JP; Tsang 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 Anal Environ Epidemiol 11: 231-252.

Klimisch HJ; Chevalier HJ; Harke HP; Dontenwill W. (1975). Uptake of carbon monoxide in blood of miniture pigs and other mammals. Toxicology 3: 301-310.

Knuckles TL; Lund AK; Lucas SN; Campen MJ. (2008). Diesel exhaust exposure enhances venoconstriction via uncoupling of eNOS. Toxicol Appl Pharmacol 230: 346-351.

Koehler RC; Jones MD; Traystman RJ. (1982). Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. American Journal of Physiology- Heart and Circulatory Physiology 243: 27-32.

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 85: 169-183.

Koken PJ; 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.

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.

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.

Kotsch K; Francuski M; Pascher A; Klemz R; Seifert M; Mittler J; Schumacher G; Buelow R; Volk HD; Tullius SG. (2006). Improved Long-Term Graft Survival after HO-1 Induction in Brain-Dead Donors. Am J Transplantation 6: 477.

Kreider JC; Blumberg MS. (2005). Geotaxis and beyond: commentary on Motz and Alberts (2005). Neurotoxicol Teratol 27: 529-533.

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.

Krewski D; Burnett RT; Goldberg MS; Hoover K; Siemiatycki J; Jerret M. (2000). Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. . Health Effects, Institute, Boston, MA.

Kruize H; Hanninen O; Breugelmans O; Lebret E; Jantunen M. (2003). Description and demonstration of the EXPOLIS simulation model: two examples of modeling population exposure to particulate matter. J ExpoAnalEnvironEpidemiol 13: 87-99.

Kuenzli 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.

Kwon HJ; Cho SH; 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.

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.

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 PM2.5, VOC, NO2 and CO in Oxford, UK. Atmos Environ 38: 6399-6410.

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.

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.

Landaw SA. (1973). The effects of cigarette smoking on total body burden and excretion rates of carbon monoxide. J Occup Med 15: 231-235.

Langan L. (1992). Portability in measuing exposure to carbon monoxide. Journal of Exposure Analysis and Environmental Epidemiology Suppl 1: 223-239.

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. (2006). Associations of traffic related air pollutants with hospitalisation for first acute myocardial infarction: the HEAPSS study. Occupational and Environmental Medicine 63: 844-851.

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: H160-167.

Lee BE; Ha EH; Park HS; Kim YJ; Hong YC; Kim H; Lee JT. (2003a). Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum Reprod 18: 638-643.

Lee IM; Tsai SS; Ho CK; Chiu HF; Yang C. (2007a). Air pollution and hospital admissions for congestive heart failure in a tropical city: Kaohsiung, Taiwan. Inhalation Toxicology 19: 899-904.

Lee IM; Tsai SS; Chang CC; Ho CK; Yang CY. (2007b). Air pollution and hospital admissions for chronic obstructive pulmonary disease in a tropical city: Kaohsiung, Taiwan. Inhalation Toxicology 19: 393-398.

Lee JT; Kim H; Song H; Hong YC; Cho YS; Shin SY; Hyun YJ; Kim YS. (2002). Air pollution and asthma among children in Seoul, Korea. Epidemiology 13: 481-484.

Lee JT; Kim H; Cho YS; Hong YC; Ha EH; Park H. (2003b). Air pollution and hospital admissions for ischemic heart diseases among individuals 64+ years of age residing in Seoul, Korea. Archives of Environmental Health 58: 617-623.

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.

Lee JT; Son JY; Cho YS. (2007c). 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. Environmental Research 105: 409-413.

Lee PJ; Jiang BH; Chin BY; Iyer NV; Alam J; Semenza GL; Choi AM. (1997). Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. J Biol Chem 272: 5375-5381.

Lee YL; Shaw CK; Su HJ; Lai JS; Ko YC; Huang SL; Sung FC; Guo YL. (2003c). Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. Eur Respir J 21: 964-970.

Leem JH; 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.

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.

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 Anal Environ Epidemiol 10: 58-65.

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.

Li CI; Daling JR; Emanuel I. (2003). Birthweight and risk of overall and cause-specific childhood mortality. Paediatr Perinat Epidemiol 17: 164-170.

Li XY; Zhang C; Wang SF; Ji YL; Wang H; Zhao L; Xu DX. (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.

Liao D; Duan Y; Whitsel EA; Zheng ZJ; Heiss G; Chinchilli VM; Lin HM. (2004). Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. American Journal of Epidemiology 159: 768-777.

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 Anal Environ Epidemiol 15: 319-328.

Lin CA; Martins MA; Farhat SC; Pope CA, 3rd; Conceicao GM; Anastacio VM; Hatanaka M; Andrade WC; Hamaue WR; Bohm GM; Saldiva PH. (1999). Air pollution and respiratory illness of children in Sao Paulo, Brazil. Paediatr Perinat Epidemiol 13: 475-488.

Lin CA; Pereira LA; Nishioka DC; Conceicao GM; Braga AL; Saldiva PH. (2004a). Air pollution and neonatal deaths in Sao Paulo, Brazil. Braz J Med Biol Res 37: 765-770.

Lin CM; Li CY; Yang GY; Mao IF. (2004b). Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. Environmental Research 96: 41-50.

Lin H; McGrath JJ. (1988). Vasodilating effects of carbon monoxide. Drug Chem Toxicol 11: 371-385.

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.

Lin M; Chen Y; Villeneuve PJ; Burnett RT; Lemyre L; Hertzman C; McGrail KM; Krewski D. (2004c). Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. American Journal of Epidemiology 159: 294-303.

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: e235-240.

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.

Lipfert F; Baty J; Miller J; Wyzga R. (2006a). PM 2.5 Constituents and Related Air Quality Variables As Predictors of Survival in a Cohort of US Military Veterans. Inhalation Toxicology 18: 645-657.

Lipfert FW; Perry HM; Miller JP; Baty JD; Wyzga RE; Carmody SE. (2000a). The Washington University-EPRI Veterans' Cohort Mortality Study. Preliminary Results. Inhalation Toxicology 12: 41-73.

Lipfert FW; Morris SC; Wyzga RE. (2000b). Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J Air Waste Manage Assoc 50: 1501-1513.

Lipfert FW; Morris SC. (2002). Temporal and spatial relations between age specific mortality and ambient air quality in the United States: regression results for counties, 1960-97. Occupational and Environmental Medicine 59: 156-174.

Lipfert FW; Wyzga RE; Baty JD; Miller JP. (2006b). 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.

Lippmann M; Ito K; Nadas A; Burnett RT. (2000). Association of particulate matter components with daily mortality and morbidity in urban populations. Res Rep Health Eff Inst: 5-72, discussion 73-82.

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.

Liu S; Krewski D; Shi Y; Chen Y; Burnett RT. (2007). Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. Journal of Exposure Science and Environmental Epidemiology 17: 426-432.

Liu Y; Fechter LD. (1995). MK-801 protects against carbon monoxide-induced hearing loss. Toxicol Appl Pharmacol 132: 196-202.

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 J (Ed.), Global Biomass Burning: Atmospheric, Climatic, and Biospheric Implications (pp. 289-304). Cambridge, Massachusetts: The MIT Press.

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.

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.

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: 666-675.

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.

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.

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.

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. Atertio Thromb Vasc Biol.

Lundh B; Cavallin-Stahl E; Mercke C. (1975). Nicotinic acid and the endogenous production of carbon monoxide. Acta Med Scand 197: 173-176.

Luomanmaki K; Coburn RF. (1969). Effects of metabolism and distribution of carbon monoxide on blood and body stores. Am J Physiol 217: 354-363.

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: 208-219.

Lyall F; Myatt L. (2002). The role of the placenta in pre-eclampsia--a workshop report. Placenta 23 Suppl A: S142-145.

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.

MacKay C; Pandow M; Wolfgang R. (1963). On the chemistry of natural radiocarbon. J geophys Res 68: 3929–3931.

MacMillan V. (1975). Regional cerebral blood flow of the rat in acute carbon monoxide intoxication. Can J Physiol Pharmacol 53: 644-650.

Mactutus CF; Fechter LD. (1984). Prenatal exposure to carbon monoxide: learning and memory deficits. Science 223: 409-411.

Mactutus CF; Fechter LD. (1985). Moderate prenatal carbon monoxide exposure produces persistent, and apparently permanent, memory deficits in rats. Teratology 31: 1.

Maheswaran R; Haining RP; Brindley P; Law J; Pearson T; Fryers PR; Wise S; Campbell MJ. (2005a). 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.

Maheswaran R; Haining RP; Brindley P; Law J; Pearson T; Fryers PR; Wise S; Campbell MJ. (2005b). Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study. Stroke 36: 239-243.

Maines MD; Kappas A. (1974). Cobalt induction of hepatic heme oxygenase; with evidence that cytochrome P-450 is not essential for this enzyme activity. Proceedings of the National Academy of Sciences 71: 4293-4297.

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.

Maisonet M; Bush TJ; Correa A; Jaakkola JJ. (2001). Relation between ambient air pollution and low birth weight in the Northeastern United States. Environ Health Perspect 109 Suppl 3: 351-356.

Manier G; Moinard J; Techoueyres P; Varene N; Guenard H. (1991). Pulmonary diffusion limitation after prolonged strenuous exercise. Respir Physiol 83: 143-153.

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.

Mannes T; Jalaludin B; Morgan G; Lincoln D; Sheppeard V; Corbett S. (2005). Impact of ambient air pollution on birth weight in Sydney, Australia. Occupational and Environmental Medicine 62: 524-530.

Manno M; Rugge M; Cocheo V. (1992). Double fatal inhalation of dichloromethane. Hum Exp Toxicol 11: 540-545.

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.

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.

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

Marthan R; Castaing Y; Manier G; Guenard H. (1985). Gas exchange alterations in patients with chronic obstructive lung disease. Chest 87: 470-475.

Martin JA; Hamilton BE; Sutton PD; Ventura SJ; Menacker F; Kirmeyer S; Munson ML. (2007). Births: final data for 2005. In National vital statistics reports. National Center for Health Statistics, Hyattsville, MD. 48-11.

Martins LC; Latorre Mdo R; Saldiva PH; Braga AL. (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.

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.

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. American Journal of Respiratory and Critical Care Medicine 171: 354-360.

McCartney ML. (1990). Sensitivity analysis applied to Coburn-Forster-Kane models of carboxyhemoglobin formation. Am Ind Hyg Assoc J 51: 169-177.

McClean PA; Duguid NJ; Griffin PM; Newth CJ; Zamel N. (1981). Changes in exhaled pulmonary diffusing capacity at rest and exercise in individuals with impaired positional diffusion. Bull Eur Physiopathol Respir 17: 179-186.

McClellan RO. (1991). CASAC Closure on the 1991 AQCD for Carbon Monoxide: US EPA-SAB-CASAC-LTR-92-015, Washington, DC.

McClellan RO. (1992). CASAC Closure on the OAQPS Staff Paper for Carbon Monoxide: US EPA-SAB-CASAC-LTR-92-016, Washington, DC.

McCoubrey WK, Jr.; Huang TJ; Maines MD. (1997). Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. Eur J Biochem 247: 725-732.

McGowan JA; Hider RN; Chacko E; Town GI. (2002). Particulate air pollution and hospital admissions in Christchurch, New Zealand. Aust N Z J Public Health 26: 23-29.

McGrath JJ. (1992). Effects of altitude on endogenous carboxyhemoglobin levels. J Toxicol Environ Health 35: 127-133.

McGrath JJ; Schreck RM; Lee PS. (1993). Carboxyhemoglobin levels in humans: effects of altitude Inhalation Toxicology 5: 241-249.

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.

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.

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.

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.

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 (Maywood) 228: 564-567.

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.

Medeiros A; Gouveia N. (2005). Relationship between low birthweight and air pollution in the city of Sao Paulo, Brazil. Rev Saude Publica 39: 965-972.

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.

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 65: 1981-1998.

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.

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.

Mensink C; Cosemans G. (2008). From traffic flow simulations to pollutant concentrations in street canyons and backyards. Environmental Modelling & Software 23: 288-295.

Mercke C; Cavallin-Stahl E; Lundh B. (1975a). Carbon monoxide production and reticulocyte count in normal women. Effect of contraceptive drugs and smoking. Acta Med Scand 198: 155-160.

Mercke C; Cavallin-Stahl E; Lundh B. (1975b). Heme catabolism during short-term treatment with phenobarbital, diazepam and oxazepam. Acta Med Scand 198: 149-154.

Mercke C; Lundh B. (1976). Erythrocyte filterability and heme catabolism during the menstrual cycle. Ann Intern Med 85: 322-324.

Mereu G; Cammalleri M; Fa 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.

Merx MW; Flogel U; Stumpe T; Godecke A; Decking UK; Schrader J. (2001). Myoglobin facilitates oxygen diffusion. FASEB J 15: 1077-1079.

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

Metzger KB; Tolbert PE; Klein M; Peel JL; Flanders WD; Mulholland JA. (2004b). Ambient air pollution and arrhythmic events in patients with implanted cardioverter defibrillators, 1993-2002. Epidemiology 15: S22-S23.

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.

Meyer J; Prien T; Van Aken H; Bone HG; 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.

Mfula AM; Kukadia V; Griffiths RF; Hall DJ. (2005). Wind tunnel modelling of urban building exposure to outdoor pollution. Atmos Environ 39: 2737-2745.

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.

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.

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. New Engl J Med 356: 447.

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. http://www.narsto.org/section.src?SID=8#5.

Moolgavkar SH. (2000a). Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. Inhalation Toxicology 12 Suppl 4: 75-90.

Moolgavkar SH. (2000b). Air pollution and daily mortality in three U.S. counties. Environ Health Perspect 108: 777-784.

Moolgavkar SH. (2003a). Air pollution and daily deaths and hospital admissions in Los Angeles and Cook Counties in Health Effects Institute Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health.

Moolgavkar SH. (2003b). Air pollution and daily mortality in two U.S. counties: season-specific analyses and exposure-response relationships. Inhalation Toxicology 15: 877-907.

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: 32804-32809.

Morse CI; Pritchard LJ; Wust RC; Jones DA; Degens H. (2008). Carbon monoxide inhalation reduces skeletal muscle fatigue resistance. Acta Physiol (Oxf) 192: 397-401.

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.

Naik JS; Walker BR. (2003). Heme oxygenase-mediated vasodilation involves vascular smooth muscle cell hyperpolarization. Am J Physiol Heart Circ Physiol 285: H220-228.

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

National Center for Health Statistics. (2007). Health, United States, 2007: With chartbook on trends in health of Americans. Center for Disease Control, Hyattsville, MD,

Ndisang JF; Tabien HE; Wang R. (2004). Carbon monoxide and hypertension. J Hypertens 22: 1057-1074.

Neas LM; Schwartz J. (1996). The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. American Journal of Respiratory and Critical Care Medicine 153: 656-664.

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.

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.

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.

Norris G; YoungPong 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.

Novelli PC; Masarie KA; Lang PM; Hall BD; Myers RC; Elkins JW. (2003). Reanalysis of tropospheric CO trends: Effects of the 1997–1998 wildfires. Journal of Geophysical Research-Atmospheres 108: 4464.

Novelli PC; Masarie KA; Atmospheric Carbon Monoxide Dry Air Mole Fractions from the NOAA ESRL Carbon Cycle Cooperative Global Air Sampling Network -V--; ftp://ftp.cmdl.noaa.gov/ccg/co/flask/event/. (2008). Atmospheric Carbon Monoxide Dry Air Mole Fractions from the NOAA ESRL Carbon Cycle Cooperative Global Air Sampling Network, 1988-2007. .

NRC. (1999). Ozone-Forming Potential of Reformulated Gasoline. National Research Council, National Academies Press, Washington, D.C.

NRC. (2003). Managing carbon monoxide pollution in meteorological and topographical problem areas. Washington, D.C.: National Academies Press.

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.

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. Environmental Research 81: 231-238.

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

Ott WR; Mage DT. (1978). Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. J Air Pollut Control Assoc 28: 911-916.

Otto DA; Benigus VA; Prah JD. (1979). Carbon monoxide and human time discrimination: failure to replicate Beard-Wertheim experiments. Aviation Space and Environmental Medicine 50: 40-43.

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.

Pankow D; Matschiner F; Weigmann HJ. (1991). Influence of aromatic hydrocarbons on the metabolism of dichloromethane to carbon monoxide in rats. Toxicology 68: 89-100.

Park H; Lee B; Ha EH; Lee JT; Kim H; Hong YC. (2002). Association of air pollution with school absenteeism due to illness. Arch Pediatr Adolesc Med 156: 1235-1239.

Park JW; Lim YH; Kyung SY; An CH; Lee SP; Jeong SH; Ju YS. (2005a). 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.

Park SK; O'Neill MS; Vokonas PS; Sparrow D; Schwartz J. (2005b). Effects of air pollution on heart rate variability: the VA normative aging study. Environ Health Perspect 113: 304-309.

Parker JD; Woodruff TJ; Basu R; Schoendorf KC. (2005). Air pollution and birth weight among term infants in California. Pediatrics 115: 121-128.

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. Journal of Geophysical Research 107: 4140.

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

Patel AP; John Moody A; Handy RD; Robert Sneyd J. (2003). Carbon monoxide exposure in rat heart: glutathione depletion is prevented by antioxidants. Biochem Biophys Res Commun 302: 392-396.

Peel JL; Tolbert PE; Klein M; Metzger KB; Flanders WD; Todd K; Mulholland JA; Ryan PB; Frumkin H. (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology 16: 164-174.

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. American Journal of Epidemiology 165: 625-633.

Pekkanen J; Brunner EJ; Anderson HR; Tiittanen P; Atkinson RW. (2000). Daily concentrations of air pollution and plasma fibrinogen in London. Occupational and Environmental Medicine 57: 818-822.

Pelham TW; Holt LE; Moss MA. (2002). Exposure to carbon monoxide and nitrogen dioxide in enclosed ice arenas. Occupational and Environmental Medicine 59: 224-233.

Penn A; Currie J; Snyder C. (1992). Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels. Eur J Pharmacol 228: 155-164.

Penney DG; Baylerian MS; Thill JE; Fanning CM; Yedavally S. (1982). Postnatal carbon monoxide exposure: immediate and lasting effects in the rat. American Journal of Physiology- Heart and Circulatory Physiology 243: 328-339.

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: H289-297.

Penney DG; Barthel BG; Skoney JA. (1984). Cardiac compliance and dimensions in carbon monoxide-induced cardiomegaly. Cardiovasc Res 18: 270-276.

Penney DG. (1988). Hemodynamic response to carbon monoxide. Environ Health Perspect 77: 121-130.

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.

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

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.

Penttinen P; Tiittanen P; Pekkanen J. (2004). Mortality and air pollution in metropolitan Helsinki, 1988--1996. Scand J Work Environ Health 30 Suppl 2: 19-27.

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.

Pesola GR; Huggins G; Sherpa TY. (2006). Abnormal predicted diffusion capacities in healthy Asians: an inequality with a solution. Respiration 73: 799-807.

Peters A; Perz S; Doring A; Stieber J; Koenig W; Wichmann HE. (1999a). Increases in heart rate during an air pollution episode. American Journal of Epidemiology 150: 1094-1098.

Peters A; Skorkovsky J; Kotesovec F; Brynda J; Spix C; Wichmann HE; Heinrich J. (2000a). Associations between mortality and air pollution in central Europe. Environ Health Perspect 108: 283-287.

Peters A; Liu E; Verrier RL; Schwartz J; Gold DR; Mittleman M; Baliff J; Oh JA; Allen G; Monahan K; Dockery DW. (2000b). Air pollution and incidence of cardiac arrhythmia. Epidemiology 11: 11-17.

Peters A; Dockery DW; Muller JE; Mittleman MA. (2001). Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103: 2810-2815.

Peters JM; Avol E; Navidi W; London SJ; Gauderman WJ; Lurmann F; Linn WS; Margolis H; Rappaport E; Gong H; Thomas DC. (1999b). A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. American Journal of Respiratory and Critical Care Medicine 159: 760-767.

Petersen LC. (1977). The effect of inhibitors on the oxygen kinetics of cytochrome c oxidase. Biochim Biophys Acta 460: 299-307.

Peterson JE; Stewart RD. (1970). Absorption and elimination of carbon monoxide by inactive young men. Archives of Environmental Health 21: 165-171.

Peterson JE; Stewart RD. (1975). Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J Appl Physiol 39: 633-638.

Pfister G; Hess PG; Emmons LK; Lamarque JF; Wiedinmyer C; Edwards DP; Pétron G; Gille JC; Sachse GW. (2005). Quantifying CO emissions from the 2004 Alaskan wildfires using MOPITT CO data. Geophys Res Lett 32: 1-5.

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.

Piantadosi CA. (2002). Biological chemistry of carbon monoxide. Antioxid Redox Signal 4: 259-270.

Piantadosi CA; Carraway MS; Suliman HB. (2006). Carbon monoxide, oxidative stress, and mitochondrial permeability pore transition. Free Radic Biol Med 40: 1332-1339.

Piantadosi CA. (2008). Carbon monoxide, reactive oxygen signaling, and oxidative stress. Free Radic Biol Med 45: 562-569.

Pirjola L; Paasonen P; Pfeiffer D; Hussein T; Hämeri K; Koskentalo T; Virtanen A; Rönkkö T; Keskinen J; Pakkanen TA. (2006). Dispersion of particles and trace gases nearby a city highway: mobile laboratory measurements in Finland. Atmos Environ 40: 867-879.

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 Manage Assoc 57: 366-379.

Pollack A; Lindhjem C; Stoeckenius T; Tran C; Mansell G; Jimenez M; Wilson G; Coulter-Burke S. (2004). Evaluation of the US EPA MOBILE6 Highway Vehicle Emissions Factor Model. ENVIRON International, Novato, CA. CRC Project E-64.

Pope CA, 3rd; 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 U.S. adults. American Journal of Respiratory and Critical Care Medicine 151: 669-674.

Pope CA, 3rd; 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. Journal of the American Medical Association 287: 1132-1141.

Prigge E; Hochrainer D. (1977). Effects of carbon monoxide inhalation on erythropoiesis and cardiac hypertrophy in fetal rats. Toxicol Appl Pharmacol 42: 225-228.

Prommer N; Schmidt W. (2007). Loss of CO from the intravascular bed and its impact on the optimised CO-rebreathing method. Eur J Appl Physiol 100: 383-391.

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 2: 97-112.

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.

Rainham DG; Smoyer-Tomic KE. (2003). The role of air pollution in the relationship between a heat stress index and human mortality in Toronto. Environmental Research 93: 9-19.

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.

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.

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

Raub JA; Benignus VA. (2002). Carbon monoxide and the nervous system. Neurosci Biobehav Rev 26: 925-940.

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.

Reeves RB; Park HK. (1992). CO uptake kinetics of red cells and CO diffusing capacity. Respir Physiol 88: 1-21.

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.

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.

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. American Journal of Epidemiology 161: 1123-1132.

Rich DQ; Mittleman MA; Link MS; Schwartz J; Luttmann-Gibson H; Catalano PJ; Speizer FE; Gold DR; Dockery DW. (2006a). Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. Environ Health Perspect 114: 120-123.

Rich DQ; Kim MH; Turner JR; Mittleman MA; Schwartz J; Catalano PJ; Dockery DW. (2006b). Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in the St Louis, Missouri metropolitan area. Occupational and Environmental Medicine 63: 591-596.

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. Inhalation Toxicology 16: 363-372.

Richardson RS; Noyszewski EA; Saltin B; Gonzalez-Alonso J. (2002). Effect of mild carboxy-hemoglobin on exercising skeletal muscle: intravascular and intracellular evidence. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 283: R1131-1139.

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. Environmental Science and Technology 37: 2084-2093.

Rigby M; Toumi R. (2008). London air pollution climatology: Indirect evidence for urban boundary layer height and wind speed enhancement. Atmos Environ 42: 4932-4947.

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. Journal of Exposure Science and Environmental Epidemiology 16: 131-137.

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.

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.

Ritz B; Yu F; Fruin S; Chapa G; Shaw GM; Harris JA. (2002). Ambient air pollution and risk of birth defects in Southern California. American Journal of Epidemiology 155: 17-25.

Ritz B; Wilhelm M; Zhao Y. (2006). Air pollution and infant death in southern California, 1989-2000. Pediatrics 118: 493-502.

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. American Journal of Epidemiology 166: 1045-1052.

Rodes C; Sheldon L; Whitaker D; Clayton A; Fitzgerald K. (1999). Measuring concentrations of selected air pollutants inside California vehicles. Final report. Sierra Research Institute, Sacramento, CA. PB--99-161028/XAB.

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.

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.

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.

Roemer WH; van Wijnen JH. (2001). Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology 12: 649-653.

Rosamond W; Flegal K; Furie K; Go A; Greenlund K; Haase N; Hailpern SM; Ho M; Howard V; Kissela B; Kittner S; Lloyd-Jones D; McDermott M; Meigs J; Moy C; Nichol G; O'Donnell C; Roger V; Sorlie P; Steinberger J; Thom T; Wilson M; Hong Y. (2008). Heart disease and stroke statistics - 2008 update - A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 117: E25-E146.

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.

Roth RA; Rubin RJ. (1976a). 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.

Roth RA; Rubin RJ. (1976b). 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.

Rothman KJ; Greenland S. (1998). Modern epidemiology (2 ed.). Philadelphia, PA: Lippincott-Raven Publishers.

Roughton FJ; 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.

Roughton FJ; Forster RE. (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange 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.

Roughton FJ. (1970). The equilibrium of carbon monoxide with human hemoglobin in whole blood. Ann N Y Acad Sci 174: 177-188.

Ruckerl R; Ibald-Mulli A; Koenig W; Schneider 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. American Journal of Respiratory and Critical Care Medicine 173: 432-441.

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.

Ryan PH; LeMasters GK. (2007). A Review of Land-use Regression Models for Characterizing Intraurban Air Pollution Exposure. Inhalation Toxicology 19: 127-133.

Ryter SW; Alam J; Choi AM. (2006). Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol Rev 86: 583-650.

Salam MT; Millstein J; Li YF; 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.

Samet JM; Dominici F; Curriero FC; Coursac I; Zeger SL. (2000a). Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 343: 1742-1749.

Samet JM; Dominici F; Zeger SL; Schwartz J; Dockery DW. (2000b). The National Morbidity, Mortality, and Air Pollution Study. Part I: Methods and methodologic issues. Res Rep Health Eff Inst: 5-14; discussion 75-84.

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.

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

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.

Sarnat SE. (2006). Factors affecting the association between ambient concentrations and personal exposures to particles and gases. Environ Health Perspect 114: 649-654.

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. Occupational and Environmental Medicine 63: 700-706.

Sartiani L; Cerbai E; Lonardo G; DePaoli P; Tattoli M; Cagiano R; Carratu MR; 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.

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. American Journal of Epidemiology 164: 505-517.

Schoenfisch WH; Hoop KA; Struelens BS. (1980). Carbon monoxide absorption through the oral and nasal mucosae of cynomolgus monkeys. Archives of Environmental Health 35: 152-154.

Schwartz J; Norris G; Larson T; Sheppard L; Claiborne C; Koenig J. (1999). Episodes of high coarse particle concentrations are not associated with increased mortality. Environ Health Perspect 107: 339-342.

Schwartz J; 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.

Schwetz BA; Smith FA; Leong BK; Staples RE. (1979). Teratogenic potential of inhaled carbon monoxide in mice and rabbits. Teratology 19: 385-392.

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

Seila RL; Lonneman WA; Meeks SA. (1989). Determination of C2 to C12 ambient air hydrocarbons in 39 US cities from 1984 through 1986. PB-89-214142/XAB, Computer Sciences Corp., Research Triangle Park, NC (USA),

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.

Sharma VS; Schmidt MR; Ranney HM. (1976). Dissociation of CO from carboxyhemoglobin. J Biol Chem 251: 4267-4272.

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.

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.

Sheppard L; Slaughter JC; Schildcrout J; Liu LJ; Lumley T. (2005). Exposure and measurement contributions to estimates of acute air pollution effects. Journal of Exposure Analysis and Environmental Epidemiology 15: 366.

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. Archives of Environmental Health 42: 108-116.

Sheps DS; Herbst MC; Hinderliter AL; Adams KF; Ekelund LG; O'Neil JJ; Goldstein GM; Bromberg PA; Dalton JL; Ballenger MN; et al. (1990). Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. Ann Intern Med 113: 343-351.

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.

Shimazu T. (2001). Half-life of blood carboxyhemoglobin. Chest 119: 661-663.

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.

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 Manage Assoc 54: 1212-1218.

Singh J. (1986). Early behavioral alterations in mice following prenatal carbon monoxide exposure. Neurotoxicology 7: 475-481.

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.

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.

Singh MP; Sharan M; Selvakumar S. (1991). A mathematical model for the computation of carboxyhaemoglobin in human blood as a function of exposure time. Philos Trans R Soc Lond B Biol Sci 334: 135-147.

Singh V; Khandelwal R; Gupta AB. (2003). Effect of air pollution on peak expiratory flow rate variability. J Asthma 40: 81-86.

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.

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.

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 Anal Environ Epidemiol 15: 153-159.

Smith MV. (1990). Comparing solutions to the linear and nonlinear CFK equations for predicting COHb formation. Math Biosci 99: 251-263.

Smith MV; Hazucha MJ; Benignus VA; Bromberg PA. (1994). Effect of regional circulation patterns on observed HbCO levels. J Appl Physiol 77: 1659-1665.

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.

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.

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.

Song R; Mahidhara RS; Liu F; Ning W; Otterbein LE; Choi AM. (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.

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.

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. Archives of Environmental Health 56: 167-174.

Steinvil A; Kordova-Biezuner L; Shapira I; Berliner S; Rogowski O. (2008). Short-term exposure to air-pollution and inflammation-sensitive biomarkers. Environmental Research 106: 51-61.

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.

Stewart RD; Newton PE; Hosko MJ; Peterson JE. (1973a). Effect of carbon monoxide on time perception. Archives of Environmental Health 27: 155-160.

Stewart RD; Peterson JE; Fisher TN; Hosko MJ; Baretta ED; Dodd HC; Herrmann AA. (1973b). Experimental human exposure to high concentrations of carbon monoxide. Archives of Environmental Health 26: 1-7.

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 Manage Assoc 52: 470-484.

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 Manage Assoc 53: 258-261.

Stieb DM; Evans GJ; Sabaliauskas K; Chen LI; Campbell ME; Wheeler AJ; Brook JR; Guay M. (2007). A scripted activity study of the impact of protective advice on personal exposure to ultra-fine and fine particulate matter and volatile organic compounds. Journal of Exposure Science and Environmental Epidemiology 18: 495-502.

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.

Stölzel M; Breitner S; Cyrys J; Pitz M; Wolke G; Kreyling W; Heinrich J; Wichmann HE; Peters A. (2006). Daily mortality and particulate matter in different size classes in Erfurt, Germany. Journal of Exposure Science and Environmental Epidemiology 17: 458-467.

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.

Storm JE; Fechter LD. (1985a). Alteration in the postnatal ontogeny of cerebellar norepinephrine content following chronic prenatal carbon monoxide. J Neurochem 45: 965-969.

Storm JE; Fechter LD. (1985b). Prenatal carbon monoxide exposure differentially affects postnatal weight and monoamine concentration of rat brain regions. Toxicol Appl Pharmacol 81: 139-146.

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.

Styka PE; Penney DG. (1978). Regression of carbon monoxide-induced cardiomegaly. American Journal of Physiology- Heart and Circulatory Physiology 235: 516-522.

Suliman HB; Carraway MS; Tatro LG; Piantadosi CA. (2007). A new activating role for CO in cardiac mitochondrial biogenesis. J Cell Sci 120: 299.

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. American Journal of Epidemiology 157: 501-509.

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.

Sun Y; Jin K; Mao XO; Zhu Y; Greenberg DA. (2001). Neuroglobin is up-regulated by and protects neurons from hypoxic-ischemic injury. Proceedings of the National Academy of Sciences 98: 15306-15311.

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.

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.

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. American Journal of Epidemiology 164: 421-433.

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.

Takeuchi A; Vesely A; Rucker J; Sommer LZ; Tesler J; Lavine E; Slutsky AS; Maleck WH; Volgyesi G; Fedorko L; Iscoe S; Fisher JA. (2000). A simple "new" method to accelerate clearance of carbon monoxide. American Journal of Respiratory and Critical Care Medicine 161: 1816-1819.

Tarkiainen TH; Timonen KL; Vanninen EJ; Alm S; Hartikainen JE; 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.

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.

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.

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. Archives of Environmental Health 57: 41-47.

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. American Journal of Physiology- Regulatory, Integrative and Comparative Physiology 288: 615-622.

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.

Thom SR; Ischiropoulos H. (1997). Mechanism of oxidative stress from low levels of carbon monoxide. Res Rep Health Eff Inst: 1-19; discussion 21-17.

Thom SR; Xu YA; Ischiropoulos H. (1997). Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem Res Toxicol 10: 1023-1031.

Thom SR; Ohnishi ST; Fisher D; Xu YA; Ischiropoulos H. (1999a). Pulmonary vascular stress from carbon monoxide. Toxicol Appl Pharmacol 154: 12-19.

Thom SR; Fisher D; Xu YA; Garner S; Ischiropoulos H. (1999b). Role of nitric oxide-derived oxidants in vascular injury from carbon monoxide in the rat. Am J Physiol 276: H984-992.

Thom SR; Fisher D; Xu YA; Notarfrancesco K; Ischiropoulos H. (2000). Adaptive responses and apoptosis in endothelial cells exposed to carbon monoxide. Proceedings of the National Academy of Sciences 97: 1305-1310.

Thom SR; Fisher D; Manevich Y. (2001a). Roles for platelet-activating factor and? NO-derived oxidants causing neutrophil adherence after CO poisoning. American Journal of Physiology- Heart and Circulatory Physiology 281: 923-930.

Thom SR; Fisher D; Manevich Y. (2001b). Roles for platelet-activating factor and *NO-derived oxidants causing neutrophil adherence after CO poisoning. Am J Physiol Heart Circ Physiol 281: H923-930.

Thom SR; Bhopale VM; Han ST; Clark JM; Hardy KR. (2006). Intravascular neutrophil activation due to carbon monoxide poisoning. American Journal of Respiratory and Critical Care Medicine 174: 1239-1248.

Thompson AJ; Shields MD; Patterson CC. (2001). Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. Archives of Environmental Health 56: 234-241.

Thompson AM; Cicerone RJ. (1986). Possible perturbations to atmospheric CO, CH4, and OH. Journal of Geophysical Research 91: 10853-10864.

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.

Thorup C; Jones CL; Gross SS; Moore LC; Goligorsky MS. (1999). Carbon monoxide induces vasodilation and nitric oxide release but suppresses endothelial NOS. American Journal of Physiology- Renal Physiology 277: 882-889.

Tikuisis P; Buick F; Kane DM. (1987a). Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO. J Appl Physiol 63: 820-827.

Tikuisis P; Madill HD; Gill BJ; Lewis WF; Cox KM; Kane DM. (1987b). A critical analysis of the use of the CFK equation in predicting COHb formation. Am Ind Hyg Assoc J 48: 208-213.

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. Occupational and Environmental Medicine 59: 129-134.

Timonen KL; Vanninen E; de Hartog J; Ibald-Mulli A; Brunekreef B; Gold DR; Heinrich J; Hoek G; Lanki T; Peters A. (2006). Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: The ULTRA study. Journal of Exposure Science and Environmental Epidemiology 16: 332-341.

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. Journal of Exposure Science and Environmental Epidemiology 17 Suppl 2: S29-35.

Tolcos M; Mallard C; McGregor H; Walker D; Rees S. (2000a). 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.

Tolcos M; McGregor H; Walker D; Rees S. (2000b). 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.

Topping DL. (1975). Acute effects of carbon monoxide on the metabolism of perfused rat liver. Biochem J 152: 425-427.

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.

Tsai SS; Huang CH; Goggins WB; Wu TN; Yang CY. (2003a). Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A 66: 1341-1349.

Tsai SS; Goggins WB; Chiu HF; Yang CY. (2003b). Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke 34: 2612-2616.

Tsai SS; Cheng MH; Chiu HF; Wu TN; Yang CY. (2006a). Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. Inhalation Toxicology 18: 549-554.

Tsai SS; Chen CC; Hsieh HJ; Chang CC; Yang CY. (2006b). Air pollution and postneonatal mortality in a tropical city: Kaohsiung, Taiwan. Inhalation Toxicology 18: 185-189.

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 (Vol. 86, pp. 3833-3839): Endocrine Soc.

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.

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.

U.S. Code. (1970). Clean Air Act, §108, air quality criteria and control techniques. Retrieved. from.

U.S. EPA. (1978). Altitude as a factor in air pollution. Office of Research and Development, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/9-78-015.

U.S. EPA. (1979a). Air quality criteria for carbon monoxide. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA-600/8-79-022.

U.S. EPA. (1979b). Assessment of Adverse Health Effects from Carbon Monoxide and Implications for Possible Modifications of the Standard. Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, NC.

U.S. EPA. (1984a). 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.

U.S. EPA. (1984b). Revised evaluation of health effects associated with carbon monoxide exposure: an addendum to the 1979 EPA air quality criteria document for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-83-033F.

U.S. EPA. (1991). Air quality criteria for carbon monoxide. EPA/600/8-90/045F, Office of Health and Environmental Assessment., Environmental Criteria and Assessment Office. Research Triangle Park, NC, Available from: NTIS, Springfield, VA, 1991. PB93-167492,

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. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA-452/R-92-004.

U.S. EPA. (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Research Triangle Park, N.C. EPA/600/P-99/001F. http://www.epa.gov/ncea/pdfs/coaqcd.pdf.

U.S. EPA. (2004). Air Quality Criteria for Particulate Matter. U.S. Environmental Protection Agency, Washington, D.C. EPA/600/P-99/002aF-bF.

U.S. EPA. (2005). Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Washington, D.C. EPA/630/P-03/001F.

U.S. EPA. (2006a). 2002 National Emissions Inventory Data and Documentation. U.S. Environmental Protection Agency, Office of Air and Radiation, Office of Air Quality Planning and Standards, Research Triangle Park, NC. http://www.epa.gov/ttn/chief/net/2002inventory.html.

U.S. EPA. (2006b). Air Quality Criteria for Ozone and Related Photochemical Oxidants. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA 600/R-05/004aF.

U.S. EPA. (2007). Documentation For The Final 2002 Mobile National Emissions Inventory - Version 3

U.S. EPA. (2008a). Inventory of U.S. Greenhouse Gas Emissions and Sinks, 1990-2006. U.S. Environmental Protection Agency, Office of Atmospheric Programs, Washington, D.C. EPA 430-R-08-005.

U.S. EPA. (2008b). Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, Research Triangle Park, NC.

U.S. EPA. (2008c). U.S. EPA's 2008 Report on the Environment (Final Report). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/R-07/045F.

U.S. EPA. (2008d). Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC.

U.S. EPA. (2008e). Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/R-08/071.

U.S. EPA. (2008f). Integrated Science Assessment for Particulate Matter, First External Review Draft. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/R-08/139.

U.S. EPA. (2008g). Integrated Science Assessment for Sulfur Oxides–Health Criteria. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/R-08/047F-FA.

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. Proceedings of the National Academy of Sciences 101: 17351-17356.

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. Atmospheric Chemistry and Physics 6: 3423–3441.

van Wijnen JH; Verhoeff AP; Jans HW; van Bruggen M. (1995). The exposure of cyclists, car drivers and pedestrians to traffic-related air pollutants. Int Arch Occup Environ Health 67: 187-193.

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: 45-52.

Vedal S; Rich K; Brauer M; White R; Petkau J. (2004). Air pollution and cardiac arrhythmias in patients with implantable cardioverter defibrillators. Inhalation Toxicology 16: 353-362.

Veen AVD; Briggs DJ; Collins S; Elliott P; Fischer P; Kingham S; Lebret E; Pryl K; Van Reeuwijk H; Smallbone K. (1997). Mapping urban air pollution using GIS: A regression-based approach. International Journal of Geographical Information Science 11: 699-718.

Verma A; Hirsch DJ; Glatt CE; Ronnett GV; Snyder SH. (1993). Carbon monoxide: a putative neural messenger. Science 259: 381-384.

Vesely AE; Somogyi RB; Sasano H; Sasano N; Fisher JA; Duffin J. (2004). The effects of carbon monoxide on respiratory chemoreflexes in humans. Environmental Research 94: 227-233.

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 70: 266-269.

Villamor E; PÉRez-VizcaÍNo F; Cogolludo AL; Conde-Oviedo J; ZaragozÁ-ArnÁEz F; LÓPez-LÓPez 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.

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 Anal Environ Epidemiol 13: 427-435.

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

Villeneuve PJ; Doiron MS; Stieb D; Dales R; Burnett RT; Dugandzic R. (2006b). Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? Allergy 61: 750-758.

Vogel JA; Gleser MA. (1972). Effect of carbon monoxide on oxygen transport during exercise. J Appl Physiol 32: 234-239.

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. European Respiratory Journal 20: 691-702.

von Klot S; Peters A; Aalto P; Bellander T; Berglind N; D'Ippoliti D; Elosua R; Hörmann A; Kulmala M; Lanki T; Löwel H; Pekkanen J; Picciotto S; Sunyer J; Forastiere F. (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.

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: 337-344.

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.

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.

Wagner JA; Horvath SM; Dahms TE. (1975). Carbon monoxide elimination. Respir Physiol 23: 41-47.

Wang R; Wang Z; Wu L. (1997). Carbon monoxide-induced vasorelaxation and the underlying mechanisms. Br J Pharmacol 121: 927-934.

Wang R. (1998). Resurgence of carbon monoxide: an endogenous gaseous vasorelaxing factor. Can J Physiol Pharmacol 76: 1-15.

Wang TN; Ko YC; Chao YY; Huang CC; Lin RS. (1999). Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. Environmental Research 81: 239-247.

Weaver LK; Howe S; Hopkins R; Chan KJ. (2000). Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. Chest 117: 801-808.

Weaver LK; Valentine KJ; Hopkins RO. (2007). Carbon Monoxide Poisoning: Risk Factors for Cognitive Sequelae and the Role of Hyperbaric Oxygen. American Journal of Respiratory and Critical Care Medicine: 200701.

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.

Webber DS; Lopez I; Korsak RA; 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.

Weinstock B; Niki H. (1972). Carbon monoxide balance in nature (Vol. 176, pp. 290-292): The American Association for the Advancement of Science.

Wellenius GA; Saldiva PHN; Batalha JRF; Krishna Murthy GG; 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 (Vol. 66, pp. 327-335): Soc Toxicology.

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.

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

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

Wellenius GA; Coull BA; Batalha JRF; Diaz EA; Lawrence J; Godleski JJ. (2006a). Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction. Inhalation Toxicology 18: 1077-1082.

Wellenius GA; Schwartz J; Mittleman MA. (2006b). Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities. Am J Cardiol 97: 404-408.

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.

Wichmann HE; 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. 1041-5505 (Print). http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11918089.

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.

Williams LJ; Rasmussen SA; Flores A; Kirby RS; Edmonds LD. (2005). Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics 116: 580-586.

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

Wilson JG; Zawar-Reza P. (2006). Intraurban-scale dispersion modelling of particulate matter concentrations: Applications for exposure estimates in cohort studies. Atmos Environ 40: 1053-1063.

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. Journal of the Air & Waste Management Association (1995) 50: 1167.

Wilson WE; Brauer M. (2006). Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. Journal of Exposure Science and Environmental Epidemiology 16: 264-274.

Wilson WE; Mar TF; Koenig JQ. (2007). Influence of exposure error and effect modification by socioeconomic status on the association of acute cardiovascular mortality with particulate matter in Phoenix. Journal of exposure science & environmental epidemiology 17: S11.

Wirkner K; Poelchen W. (1996). Influence of long-term ethanol treatment on rat liver aniline and p-nitrophenol hydroxylation. Alcohol 13: 69-74.

Wittenberg BA; Wittenberg JB; Caldwell PR. (1975). Role of myoglobin in the oxygen supply to red skeletal muscle. J Biol Chem 250: 9038-9043.

Wittenberg BA; Wittenberg JB. (1993). Effects of carbon monoxide on isolated heart muscle cells. Health Effects Institute, Boston, Massachusetts. Report No. 62. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8155298.

Wollmann HA. (1998). Intrauterine growth restriction: Definition and etiology. Hormone Res 49: 1-6.

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.

Wu L; Wang R. (2005). Carbon monoxide: endogenous production, physiological functions, and pharmacological applications. Pharmacol Rev 57: 585-630.

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

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.

Yang CY; Chang CC; Chuang HY; Tsai SS; Wu TN; Ho CK. (2004a). Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. Environ Int 30: 519-523.

Yang CY; Chen YS; Yang CH; Ho SC. (2004b). Relationship between ambient air pollution and hospital admissions for cardiovascular diseases in kaohsiung, taiwan. J Toxicol Environ Health A 67: 483-493.

Yang CY; Hsieh HJ; Tsai SS; Wu TN; Chiu HF. (2006). Correlation between air pollution and postneonatal mortality in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A 69: 2033-2040.

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 70: 111-117.

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 70: 1214-1219.

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. Inhalation Toxicology 15: 1297-1308.

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. Environmental Research 99: 99-105.

Yoshiki N; Kubota T; Aso T. (2001). Identification of heme oxygenase in human endometrium. J Clin Endocrinol Metab 86: 5033-5038.

Young LJ; Caughey WS. (1986). Oxygenation of carbon monoxide by bovine heart cytochrome c oxidase. Biochemistry 25: 152-161.

Yu O; Sheppard L; Lumley T; Koenig JQ; Shapiro GG. (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.

Zamudio S; Palmer SK; Regensteiner JG; Grindlay Moore L. (1995). High altitude and hypertension during pregnancy. Am J Hum Biol 7: 183-193.

Zanobetti A; Schwartz J; Ridker PM. (2004a). Air pollution and markers of cardiovascular risk. Epidemiology 15: S22.

Zanobetti A; Canner MJ; Stone PH; Schwartz J; Sher D; Eagan-Bengston E; Gates KA; Hartley LH; Suh H; Gold DR. (2004b). Ambient pollution and blood pressure in cardiac rehabilitation patients. Circulation 110: 2184-2189.

Zanobetti A; Schwartz J. (2006). Air pollution and emergency admissions in Boston, MA. J Epidemiol Community Health 60: 890-895.

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.

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. J Reprod Immunol 69: 35-52.

Zevin S; Saunders S; Gourlay SG; Jacob P; Benowitz NL. (2001). Cardiovascular effects of carbon monoxide and cigarette smoking. J Am Coll Cardiol 38: 1633-1638.

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.

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.

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.

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.

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.

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.