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Third External Review Draft of Air Quality Criteria for Particulate Matter (April, 2002)

Volume II

Air Quality Criteria for Particulate Matter

Volume II

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

DISCLAIMER

This document is an external review draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

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

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

1   This Third External Review Draft of revised Air Quality Criteria for Particulate Matter

2   assesses new scientific information that has become available mainly between early 1996 through

3   December 2001. The present draft is being released for public comment and review by the Clean

4   Air Scientific Advisory Committee (CASAC) to obtain comments on the organization and

5   structure of the document, the issues addressed, the approaches employed in assessing and

6   interpreting the newly available information on PM exposures and effects, and the key findings

7   and conclusions arrived at as a consequence of this assessment. Public comments and CASAC

8   review recommendations will be taken into account in making any appropriate further revisions

9   to this document for incorporation into a final draft. Evaluations contained in the present

10   document will be drawn on to provide inputs to associated PM Staff Paper analyses prepared by

11   EPA's Office of Air Quality Planning and Standards (OAQPS) to pose alternatives for

12   consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of

13   decisions on potential retention or revision of the current PM NAAQS.

14   Preparation of this document was coordinated by staff of EPA's National Center for

15   Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific

16   staff, together with experts from other EPA/ORD laboratories and academia, contributed to

17   writing of document chapters; and earlier drafts of this document were reviewed by experts from

18   federal and state government agencies, academia, industry, and NGO's for use by EPA in support

19   of decision making on potential public health and environmental risks of ambient PM. The

20   document describes the nature, sources, distribution, measurement, and concentrations of PM in

21   outdoor (ambient) and indoor environments. It also evaluates the latest data on human exposures

22   to ambient PM and consequent health effects in exposed human populations (to support decision

23   making regarding primary, health-related PM NAAQS). The document also evaluates ambient

24   PM environmental effects on vegetation and ecosystems, visibility, and man-made materials, as

25   well as atmospheric PM effects on climate change processes associated with alterations in

26   atmospheric transmission of solar radiation or its reflectance from the Earth's surface or

27   atmosphere (to support decision making on secondary PM NAAQS).

28   The NCEA of EPA acknowledges the contributions provided by authors, contributors, and

29   reviewers and the diligence of its staff and contractors in the preparation of this document.

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Abbreviations and Acronyms

σ_{abs}	light-absorption coefficient
σ_{ag}	light-absorption coefficient of gases
σ_{ap}	light-absorption coefficient of particles
σ_{ext}	light-extinction coefficient
σ_{g}	geometric standard deviation
σ_{scat}	light-scattering coefficient
σ_{sg}	light-scattering coefficient of gases
σ_{sp}	light-scattering coefficient of particles
4-POBN	α-(4-pyridyl-1-oxide)-N-tert-butylnitrone
A	alveolar
AAS	atomic absorption spectrophotometry
ACGIH	American Conference of Governmental Industrial Hygienists
AD	
ADS	annular denuder system
AES	atomic emission spectroscopy
AIRS	Aerometric Information Retrieval System
AM	alveolar macrophages
AQCD	Air Quality Criteria Document
AQI	Air Quality Index
AQRV	Air Quality Related Values
ARIES	Aerosol Research and Inhalation Epidemiology Study
ASOS	Automated Surface Observing System
ATDM	aerosol and toxic deposition model
ATOFMS	time-of-flight mass spectrometer
b	
B_a	absorption coefficient

BAD	brachial artery diameter
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BAUS	brachial artery ultrasonography
BC	black carbon (see also CB)
BW	bronchial wash
BYU	Bringham Young University
C	apparent contrast
Ca^{+2}	calcium
CAA	Clean Air Act
CAAM	continuous ambient mass monitor
CAMNET	
CAPs	concentrated ambient particles
CARB	California Air Resources Board
CASAC	Clean Air Scientific Advisory Committee
CASTNet	Clean Air Status and Trends Network
CAT	computer-aided tomography
CB	carbon black
C_B	base cation
CC	carbonate carbon
CCl_4	carbon tetrachloride
CCPM	continuous coarse particle monitor
CCSEM	computer-controlled scanning electron microscopy
CEN	European Standardization Committee
CF	Cystic Fibrosis
CFA	coal fly ash
CFCs	chlorofluorocarbons
CFD	computational fluid dynamics

CFR	Code of Federal Regulations
CH$_2$O	formaldehyde
CIF	charcoal-impregnated cellulose fiber
CL	chemiluminescence
CMAQ	Community Multi-Scale Air Quality
CMB	chemical mass balance
CMD	count mean diameter
CMP	copper smelter dust
CMSA	Consolidated Metropolitan Statistical Area
C$_o$	initial contrast
CO	carbon monoxide
CO CD	Air Quality Criteria Document for Carbon Monoxide
COPD	chronic obstructive pulmonary disease
CPC	condensation particle counter
CPZ	capsazepine
CR	concentration-response
CRP	Coordinated Research Program
CSIRO	
CSMCS	Carbonaceous Species Methods Comparison Study
CTM	chemistry-transport model
CV	coefficient of variation
D$_{50}$	
D$_a$	
DAQM	Denver Air Quality Model
DCFH	dichlorofluorescin
DE	deposition efficiencies
DE	diesel exhaust
DEF	Deferoxamine

DEP	diesel exhaust particles
DHR	dihydrorhodamine-123
DMS	dimethyl sulfide
DMTU	dimethylthiourea
DOFA	domestic oil fly ash
DPM	diesel particulate matter
DRG	dorsal root ganglia
dv	deciview index
EAD	electrical aerosol detector
EC	elemental carbon
ECAO	Environmental Criteria and Assessment Office
ECG	electrocardiogram
EDXRF	energy dispersive X-ray fluorescence
EGA	evolved gas analysis
EGF	epidermal growth factor
ELSIE	Elastic Light Scattering and Interactive Efficiency
ERK	extracellular receptor kinase
ESP	electrostatic precipitator
ESR	electron spin resonance
ET	extrathoacic
ETS	environmental tobacco smoke
EU	endotoxin units
EXPOLIS	
F	flux
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FID	flame ionization detection
FMD	flow-mediated dilation

FPD	flame photometric detector
FRM	Federal Reference Method
g SO_2	gaseous sulfur dioxide
GC	gas chromatography
GCMs	General Circulation Models
GCVTC	Grand Canyon Visibility Transport Commission
GG/MSD	gas chromatography/mass-selective detection
GHG	greenhouse gases
GMCSF	granulocyte macrophage colony stimulating factor
GMPD	geometric mean particle diameter
GSD	geometric standard deviation (see also σ_g)
GSH	glutathione
H_2SO_4	sulfuric acid
HAAQS	
HDM	house dust mite
HDS	honeycomb denuder/filter pack sampler
HEADS	Harvard-EPA Annular Denuder Sampler
HEI	Health Effects Institute
hivol	High blume sampler
HNO_3	nitric acid
HR	heart rate
HTGC-MS	high temperature gas chromotography-mass spectrometry
I	radiance
IκBα	inhibitory kappa B alpha
I_b	apparent radiance of the background
I_{bt}	transmitted radiance of the background
IC	ion chromatography
ICAM-1	intercellular adhesion molecule-1

ICP	inductively coupled plasma
ICRP	International Commission on Radiological Protection
Ie	equilibrium radiance or source function
IFS	Integrated Forest Study
IgE	immunoglobin E
IgG	immunoglobin G
IL	interleukin
IMPROVE	Interagency Monitoring of Protected Visual Environments
INAA	instrumental neutron activation analysis
IOVPS	integrated organic vapor/particle sampler
ip	intraperitoneal
I_p	path radiance
IPCC	Intergovernmental Panel on Climate Change
IPM	inhalable particulate matter
IPN	Inhalable Particulate Network
ISO	International Standards Organization
I_t	transmitted radiance
JNK	c-jun N-terminal kinase
J_{scp}	light scattering by coarse particles
J_{sfp}	light scattering by fine particles
J_{spd}	light scattering coefficient of particles under dry conditions
J_{spw}	light scattering coefficient of particles under humid conditions
K	Koschmieder constant
K^+	potassium ion
KOH	potassium hydroxide
LAI	leaf area indices
LFA-1	leukocyte function-associated antigen-1
LN	lymph nodes

LoS	low sulfur
lpm, Lpm, L/min	liters per minute
LPS	lipopolysaccharide
LWCA	liquid water content analyzer
MAA	mineral acid anion
MAACS	Metropolitan Acid Aerosol Characterization Study
MADPro	Mountain Acid Deposition Program
MAPK	mitogen-activated protein kinase
MAQSIP	page 3-83
MCM	mass concentrations monitor
MCT	monocrotaline
MEK	mitogen-activated protein kinase
MIP	macrophage inflammatory protein
Mm	megameters
MMAD	mean median aerodynamic diameter (see σ_g)
MMD	mass median diameter
MMPs	matrix metalloproteinases
MOUDI	micro-orifice uniform deposit impactor
MPL	multipath lung
MPO	myeloperoxidase
MS	mass spectroscopy
MSA	methane sulfonic acid
MSAs	metropolitan statistical areas
MSH	Mount St. Helens
MSP	
NAC	N-acetylcysteine (antioxidant)
NAL	nasal lavage fluid
NAMS	National Ambient Monitoring Stations

NaN_3	sodium azide
NAPAP	National Acid Precipitation Assessment Program
NAPRMN	
NARSTO	
NAST	National Assessment Synthesis Team
NCRPM	National Council on Radiation Protection and Measurements
ND	NIST diesel (also, not determined)
NDDN	National Dry Deposition Network
NDIR	nondispersive infrared spectrophotometry
NESCAUM	Northeast States for Coordinated Air Use Management
NF	nuclear factor
NF-κB	nuclear factor kappa B
NFRAQS	North Frontal Range Air Quality Study
NH_3	ammonia
NH_4^+	ammonium
$(NH_4)_2 SO_4$	ammonium sulfate
$NH_4H_2SO_4$	ammonium acid sulfate
NHBE	normal human bronchial epithelial
NIOSH	
NIR	
NIST	National Institute of Standards and Technology
NMD	nitroglycerine-mediated dilation
NMD	number mean diameter
NMRI	Naval Medical Research Institute
NO	nitrogen oxide
NO_2	nitrogen dioxide
NO_3^-	nitrate
NOPL	naso-oro-pharyngo-laryngeal

NO_x	nitrogen oxides
NPP	net primary production
NRC	National Research Council
NuCM	nutrient cycling model
O_3	ozone
OAA	Ottowa ambient air
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
OC	organic carbon
OFA	oil fly ask
OH^-	hydroxyl ion
ORD	Office of Research and Development
OVA	ovalbumin
p	partial pressure
$p\,SO_4^{2-}$	particulate sulfate
PAH	polynuclear aromatic hydrocarbon
PAHs	polycyclic aromatic hydrocarbons
PAN	peroxyacetyl nitrate
PAR	photosynthetically active radiation
PB	polymyxin-B
PBL	planetary boundary layer
PBY	
PC	pyrolitic carbon
PC	particle concentrator
PC-BOSS	Particulate Concentrator-Brigham Young University Organic Sampling System
PCA	principal component analysis
PCBs	polychloronated biphenyls

PCDD	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzofurans
PCM	particle composition monitor
pdf	probability density functions
PDGF	platelet-derived growth factor
PEM	Personal Environmental Monitor
PESA	proton elastic scattering analysis
PFA	
PIXE	proton induced X-ray emission
PM	particulate matter
PM AQCD	PM Air Quality Criteria Document
$PM_{(10-25)}$	coarse particulate matter
$PM_{2.5}$	fine particulate matter
PMF	positive matrix factorization
PMN	polymorphonuclear leukocytes
p^o	equilibrium vapor pressure
poly I:C	polyionosinic-polycytidilic acid
POP	persistent organic pollutant
PROBDET	Probability of Detection Algorithm
PTEAMS	
PTEP	PM_{10} Technical Enhancement Program
PTFE	polytetrafluoroethylene
PTFE	polytetrafluoroethylene
PUF	polyurethane foam
Q	respiratory flow rates
Qabs	efficiency of absorption
Qext	efficiency of extinction
Qscat	efficiency of scattering

r_a	aerodynamic resistance
RAAS	
RADM	Regional Acid Deposition Model
RAMS	Real-Time Air Monitoring System
RAMS	Regional Air Monitoring Study
RAPS	Regional Air Pollution Study
r_b	boundary layer resistance
r_c	canopy resistance
REMSAD	Regulatory Modeling System for Aerosols and Deposition
RFO	residual fuels oils
RH	relative humidity
ROFA	residual oil fly ash
ROFA	residual oil fly ash
ROME	Reactive and Optics Model Emissions
ROS	reactive oxygen species
RPM	respirable particulate matter
RPM	Regional Particulate Model
RTE	rat tracheal epithelial
RTP	Research Triangle Park
S	saturation ratio
SA	Sierra Anderson
SAD	small airway disease
SASS	
SCAQS	Southern California Air Quality Study
SCC	
SCOS	Southern California Ozone Study
sd	standard deviation
SEM	scanning electron microscopy

SES	sample equilibration system
SEV	Sensor Equivalent Visibility
SH	spontaneously hypertensive
SIP	State Implementation Plans
SIXE	synchrotron induced X-ray emission
SL	stochastic lung
SLAMS/NAMS	
SLAMS	State and Local Air Monitoring Stations
SLE	St. Louis encephalitis
SMPS	scanning mobility particle sizer
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SOA	
SOC	semivolatile organic compounds
SoCAB	South Coast Air Basin
SOD	superoxide dismutase
SOPM	secondary organic particulate matter
SP	Staff Paper
SPM	synthetic polymer monomers
SRI	
SRM	standard reference method
SSM	solid sampler module
Stk	Stokes number
SUVB	solar ultraviolet B radiation
SVOC	semivolatile organic compounds
SWMMC	Southwest Metropolitan Mexico City
T(CO)	core temperature
TB	tracheabronchial

TDF	total deposition fraction
TDMA	Tandem Differential Mobility Analyzer
TEOM	tapered element oscillating microbalance
TEOMs	
TIMP	tissue inhibitor of metaloproteinase
TLN	
TNF	tumor necrosis factor
TOFMS	aerosol time-of-flight mass spectroscopy
TOR	thermal/optical reflectance
TOT	thermal/optical transmission
TPM	thoracic particulate matter
TRXRF	total reflection X-ray fluorescence
TSI	
TSP	total suspended particulates
UAM-V	Urban Airshed Model Version V
UCM	unresolved complex mixture
ufCB	ultrafine carbon black
UFP	ultrafine fluorospheres
UNEP	United Nations Environment Programme
URG	University Research Glassware
USGCRP	U.S. Global Change Research Program
UVD	Utah Valley dust
VAPS	Versatile Air Pollution Samplers
VASM	Visibility Assessment Scoping Model
VBE	Japanese B encephalitis
VCAM-1	vascular cell adhesion molecule-1
V_d	deposition velocity
VDI	

VOC	volatile organic compounds
V_s	sedimentation velocity
V_t	turbulent diffusion velocity
V_t	tidal volume
WC	tungsten carbide
WEE	western equine encephalitis
WINS	Well Impactor Ninety-Six
WIS	Wistar
WKY	Wistar-Kyoto
WMO	World Meteorological Organization
Wo	single scattering albedo
WRAC	Wide Range Aerosol Classifier
X-XRF	synchrotron induced X-ray fluorescence
XAD	polystyrene-divinyl benzene
XRF	X-ray fluorescence
μ^*	

6. DOSIMETRY OF PARTICULATE MATTER

6.1 INTRODUCTION

A basic principle in health effects evaluation is that the dose delivered to the target site of concern, rather than the external exposure, is the proximal cause of any biological response. Characterization of the exposure-dose-response continuum for particulate matter (PM), a fundamental objective of any dose-response assessment for evaluation of health effects, requires the elucidation and understanding of the mechanistic determinants of inhaled particle dose. Furthermore, dosimetric information is critical to an effective extrapolation to humans of health effects demonstrated by toxicological studies using experimental animals and for comparison of results from controlled clinical studies involving different types of human subjects, e.g., those with preexisting respiratory disease and normals. Dosimetry provides a critical link in evaluating the relevance of health effects found in animal models of susceptible humans because it allows for discrimination between actual susceptibility differences from those due to differences in sites of particle action.

Dose to target tissue is dependent initially on the deposition of particles within the respiratory tract. Particle deposition refers to the removal of particles from their airborne state because of their aerodynamic, thermodynamic, and/or electrostatic behavior. Once particles have deposited onto the surfaces of the respiratory tract, they are subsequently subjected to either absorptive or nonabsorptive particulate removal processes. This may result in their removal from airway surfaces, as well as their removal, to varying degrees, from the respiratory tract itself. The deposited PM thus cleared from initial deposition sites is said to have undergone translocation. Clearance of deposited particles depends upon the initial site of deposition and upon the physicochemical properties of the particles, both of which impact upon specific translocation pathways. Retained particle burdens are determined by the dynamic relationship between deposition and clearance rates.

This chapter is concerned with particle dosimetry, the study of the deposition, translocation, clearance, and retention of particles within the respiratory tract and extrapulmonary tissues. It summarizes basic concepts as presented in the 1996 EPA document, Air Quality Criteria for

1   Particulate Matter or "PM AQCD" (U.S. Environmental Protection Agency, 1996), specifically

2   in Chapter 10; and it updates the state of the science based upon new literature appearing since

3   publication of the 1996 PM AQCD. Although our understanding of the basic mechanisms

4   governing deposition and clearance of inhaled particles has not changed, there has been

5   significant additional information on the role of certain biological determinants of the

6   deposition/clearance processes, such as gender and age. Also, the understanding of regional

7   dosimetry and the particle size range over which this has been evaluated has been expanded.

8   The dose from inhaled particles deposited and retained in the respiratory tract is governed

9   by a number of factors. These include exposure concentration and exposure duration, respiratory

10   tract anatomy and ventilatory parameters, and by physicochemical properties of the particles

11   themselves (e.g., particle size, hygroscopicity, solubility). The basic characteristics of particles

12   as they relate to deposition and retention, as well as anatomical and physiological factors

13   influencing particle deposition and retention, were discussed in depth in the 1996 PM AQCD.

14   Thus, in this current chapter, only an overview of basic information related to one critical factor

15   in deposition, namely particle size, is provided (Section 6.1.1), so as to allow the reader to

16   understand the different terms used in the remainder of this chapter and in subsequent ones

17   dealing with health effects. This is followed, in Section 6.1.2, by a basic overview of respiratory

18   tract structure as it relates to deposition evaluation. The ensuing major sections of this chapter

19   provide updated information on particle deposition, clearance, and retention in the respiratory

20   tract of humans, as well as laboratory animals, which are useful in the evaluation of PM health

21   effects. Issues related to the phenomenon of particle overload as it may apply to human exposure

22   and the use of instillation as an exposure technique to evaluate PM health effects also are

23   discussed. The final sections of the chapter deal with mathematical models of particle

24   disposition in the respiratory tract.

25   It must be emphasized that any dissection into discrete topics of factors that control dose

26   from inhaled particles tends to mask the dynamic and interdependent nature of the intact

27   respiratory system. For example, although deposition is discussed separately from clearance

28   mechanisms, retention (i.e., the actual amount of particles found in the respiratory tract at any

29   point in time) is, as noted previously, determined by the relative rates of both deposition and

30   clearance. Thus, assessment of overall dosimetry requires integration of these various

31   components of the overall process. In summarizing the literature on particle dosimetry, when

1   applicable, changes from control are described if they were statistically significant at a

2   probability (p) value less than 0.05 (i.e., $p < 0.05$). When trends are described, an attempt will be

3   made to provide the actual p values given in the published reports.

4

6.1.1 Size Characterization of Inhaled Particles

6   Information about particle size distribution is important in the evaluation of effective

7   inhaled dose. This section summarizes particle attributes requiring characterization and provides

8   some general definitions important in understanding particle fate within the respiratory tract.

9   Particles exist in the atmosphere as components of aerosols, which are airborne suspensions

10   of finely dispersed solid or liquid particles. Because aerosols can consist of almost any material,

11   their description in simple geometric terms can be misleading unless important factors relating to

12   constituent particle size, shape, and density are considered. Although the size of particles within

13   aerosols can be described based on actual physical measurements (such as those obtained with a

14   microscope), in many cases it is better to use some equivalent diameter in place of the physical

15   diameter. The most commonly used metric is aerodynamic equivalent diameter (AED), whereby

16   particles of differing geometric size, shape, and density are compared in terms of aerodynamic

17   behavior (i.e., terminal setting velocity) to particles that are unit density (1 gm/cm^3) spheres. The

18   aerodynamic behavior of unit density spherical particles constitutes a useful standard by which

19   many types of particles can be compared in terms of certain deposition mechanisms. (See

20   Chapter 2 for a more complete discussion.)

21   It is important to note that most aerosols present in natural and work environments are

22   polydisperse. This means that the constituent particles within an aerosol have a range of sizes

23   and are more appropriately described in terms of a size distribution parameter. The lognormal

24   distribution (i.e., the situation in which the logarithms of particle diameter are distributed

25   normally) can be used for describing size distributions of most aerosols. In linear form, the

26   logarithmic mean is the median of the distribution, and the metric of variability around this

27   central tendency is the geometric standard deviation (σ_g). The σ_g, a dimensionless term, is the

28   ratio of the 84th (or 16th) % particle size to the 50th % size. Thus, the only two parameters

29   needed to describe a log normal distribution of particle sizes for a specific aerosol are the median

30   diameter and the geometric standard deviation. However, the actual size distribution may be

31   obtained in various ways. For example, when a distribution is described by counting particles,

1   the median is called the count median diameter (CMD). On the other hand, the median of a

2   distribution based on particle mass in an aerosol is the mass median diameter (MMD). When

3   using aerodynamic diameters, a term that is encountered frequently is mass median aerodynamic

4   diameter (MMAD), which refers to the median of the distribution of mass with respect to

5   aerodynamic equivalent diameter. Most of the present discussion will focus on MMAD because

6   it is the most commonly used measure of aerosol distribution. However, alternative distributions

7   should be used for particles with actual physical sizes below about 0.5 μm because, for these,

8   aerodynamic properties become less important. One such metric is thermodynamic-equivalent

9   size, which is the diameter of a spherical particle that has the same diffusion coefficient in air as

10   the particle of interest.

11

12   ## 6.1.2 Structure of the Respiratory Tract

13   A detailed discussion of respiratory tract structure was provided in the 1996 PM AQCD

14   (U.S. Environmental Protection Agency, 1996), and only a brief synopsis is presented here.

15   For dosimetry purposes, the respiratory tract can be divided into three regions (Figure 6-1):

16   (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists

17   of head airways (i.e., nasal and oral passages) through the larynx and represents the areas through

18   which inhaled air first passes. In humans, inhalation can occur through the nose or mouth (or

19   both, known as oronasal breathing). However, most laboratory animals commonly used in

20   respiratory toxicological studies are obligate nose breathers.

21   From the ET region, inspired air enters the TB region at the trachea. From the level of the

22   trachea, the conducting airways then undergo branching for a number of generations. The

23   terminal bronchiole is the most peripheral of the distal conducting airways and these lead,

24   in humans, to the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (all of which

25   comprise the A region). All of the conducting airways, except the trachea and portions of the

26   mainstem bronchi, are surrounded by parenchymal tissue. This is composed primarily of the

27   alveolated structures of the A region and associated blood and lymphatic vessels. It should be

28   noted that the respiratory tract regions are comprised of various cell types and that there are

29   distinct differences in the cells of airway surfaces in the ET, TB, and A regions. Although a

30   discussion of cellular structure of the respiratory tract is beyond the scope of this section, details

31   may be found in a number of sources (e.g., Crystal et al., 1997).
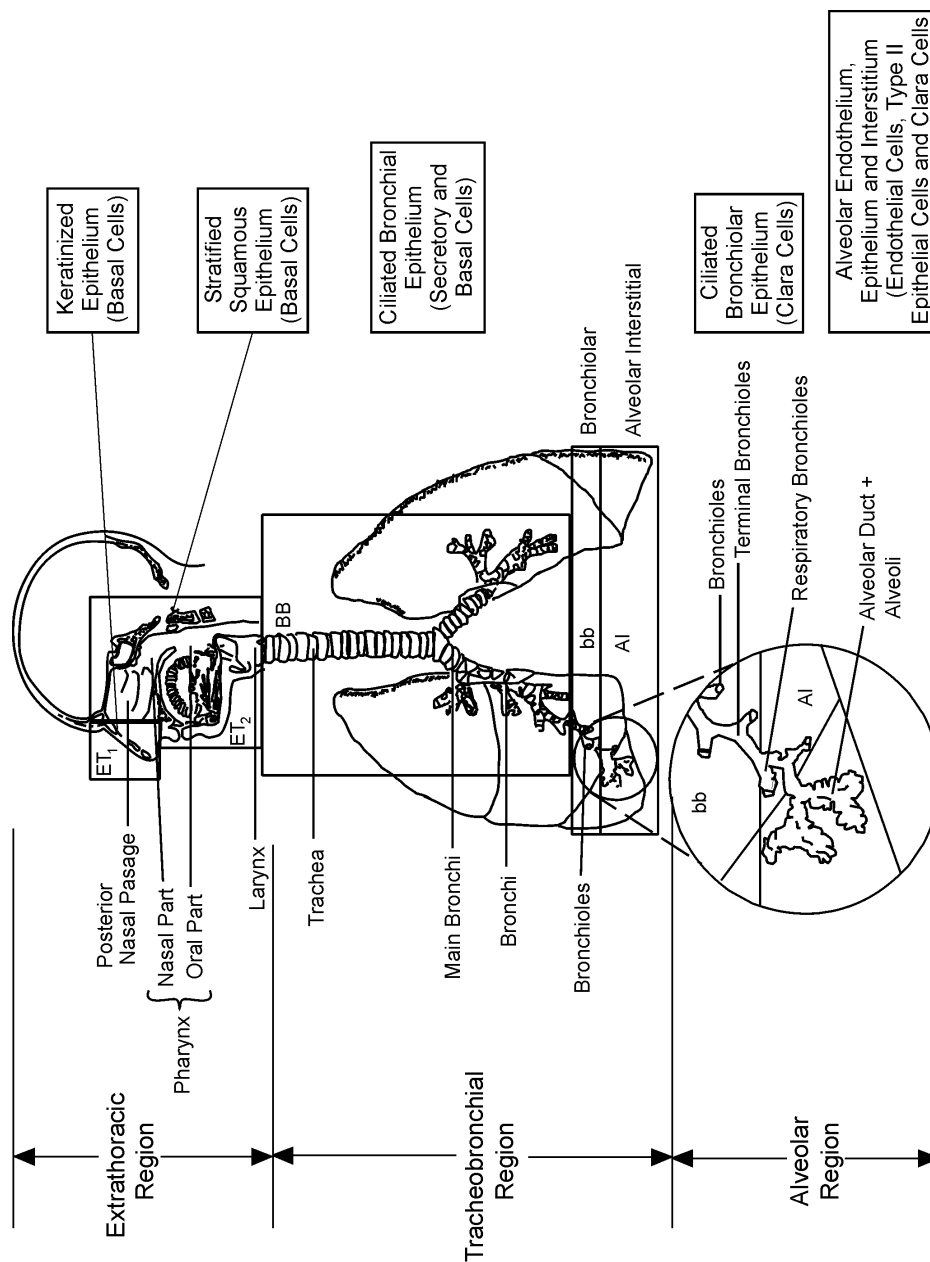
Figure 6-1. Diagrammatic representation of respiratory tract regions in humans.

Source: U.S. Environmental Protection Agency (1996).

6.2 PARTICLE DEPOSITION

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

6.2.1 Mechanisms of Deposition

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

Sudden changes in airstream direction and velocity cause particles to fail to follow the streamlines of airflow. As a consequence, the particles contact, or impact, onto airway surfaces. The ET and upper TB airways are characterized by high air velocities and sharp directional changes and, thus, dominate as sites of inertial impaction. Impaction is a significant deposition mechanism for particles larger than 1 μm AED.

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

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

1   The particle size region around 0.2 to 1.0 μm frequently is described as consisting of

2   particles that are small enough to be minimally influenced by impaction or sedimentation and

3   large enough to be minimally influenced by diffusion. Such particles are the most persistent in

4   inhaled air and undergo the lowest extent of deposition in the respiratory tract.

5   Interception is deposition by physical contact with airway surfaces. The interception

6   potential of any particle depends on its physical size, and fibers are the chief concern in relation

7   to the interception process. Their aerodynamic size is determined predominantly by their

8   diameter, but their length is the factor that influences probability of interception deposition.

9   Electrostatic precipitation is deposition related to particle charge. The minimum charge an

10   aerosol particle can have is zero. This condition rarely is achieved because of the random

11   charging of aerosol particles by air ions. Aerosol particles will acquire charges from these ions

12   by collisions with them because of their random thermal motion. Furthermore, many laboratory-

13   generated aerosols are charged. Such aerosols will generally lose their charge as they attract

14   oppositely charged ions, and an equilibrium state of these competing processes eventually is

15   achieved. This Boltzmann equilibrium represents the charge distribution of an aerosol in charge

16   equilibrium with bipolar ions. The minimum amount of charge is very small, with a statistical

17   probability that some particles within the aerosol will have no charge and others will have one or

18   more positive and negative charges.

19   The electrical charge on some particles will result in an enhanced deposition over what

20   would be expected from size alone. This results from image charges induced on the surface of

21   the airway by these particles or to space-charge effects, whereby repulsion of particles containing

22   like charges results in increased migration toward the airway wall. The effect of charge on

23   deposition is inversely proportional to particle size and airflow rate. This type of deposition is

24   often small compared to the effects of turbulence and other deposition mechanisms, and it

25   generally has been considered to be a minor contributor to overall particle deposition. However,

26   a study by Cohen et al. (1998), employing hollow airway casts of the human tracheobronchial

27   tree to assess deposition of ultrafine (0.02 μm) and fine (0.125 μm), particles found the

28   deposition of singly charged particles to be 5 to 6 times that of particles having no charge and

29   2 to 3 times that of particles at Boltzmann equilibrium. This suggests that electrostatic

30   precipitation may, in fact, be a significant deposition mechanism for ultrafine, and some fine,

31   particles within the TB region.

6.2.2 Deposition Patterns in the Human Respiratory Tract

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

Ambient air often contains particles too massive to be inhaled. The descriptor "inhalability" is used to denote the overall spectrum of particle sizes that are potentially capable of entering the respiratory tract. Inhalability is defined as the ratio of the number concentration of particles of a certain aerodynamic diameter that are inspired through the nose or mouth to the number concentration of the same diameter particle present in ambient air (International Commission on Radiological Protection, 1994). In general, for humans, unit density particles >100 μm diameter have a low probability of entering the mouth or nose in still air, but there is no sharp cutoff to zero probability. Also, there is no lower limit to inhalability, so long as the particle exceeds a critical size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties, in contrast to those of free ions or gas molecules.

6.2.2.1 Total Respiratory Tract Deposition

Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 6-2. These data were obtained by various investigators using different sizes of spherical test particles in healthy male adults under different ventilation conditions; the large standard deviations reflect interindividual and breathing pattern-related variability of deposition efficiencies. Deposition in the ET region with nose breathing is generally higher than that with mouth breathing because of the superior filtration capabilities of the nasal passages, resulting in somewhat higher total deposition with mouth breathing for particles > 1μm. For particles with aerodynamic diameters greater than 1 μm, deposition is governed by impaction and sedimentation, and it increases with increasing AED. When AED is >10 μm, almost all inhaled
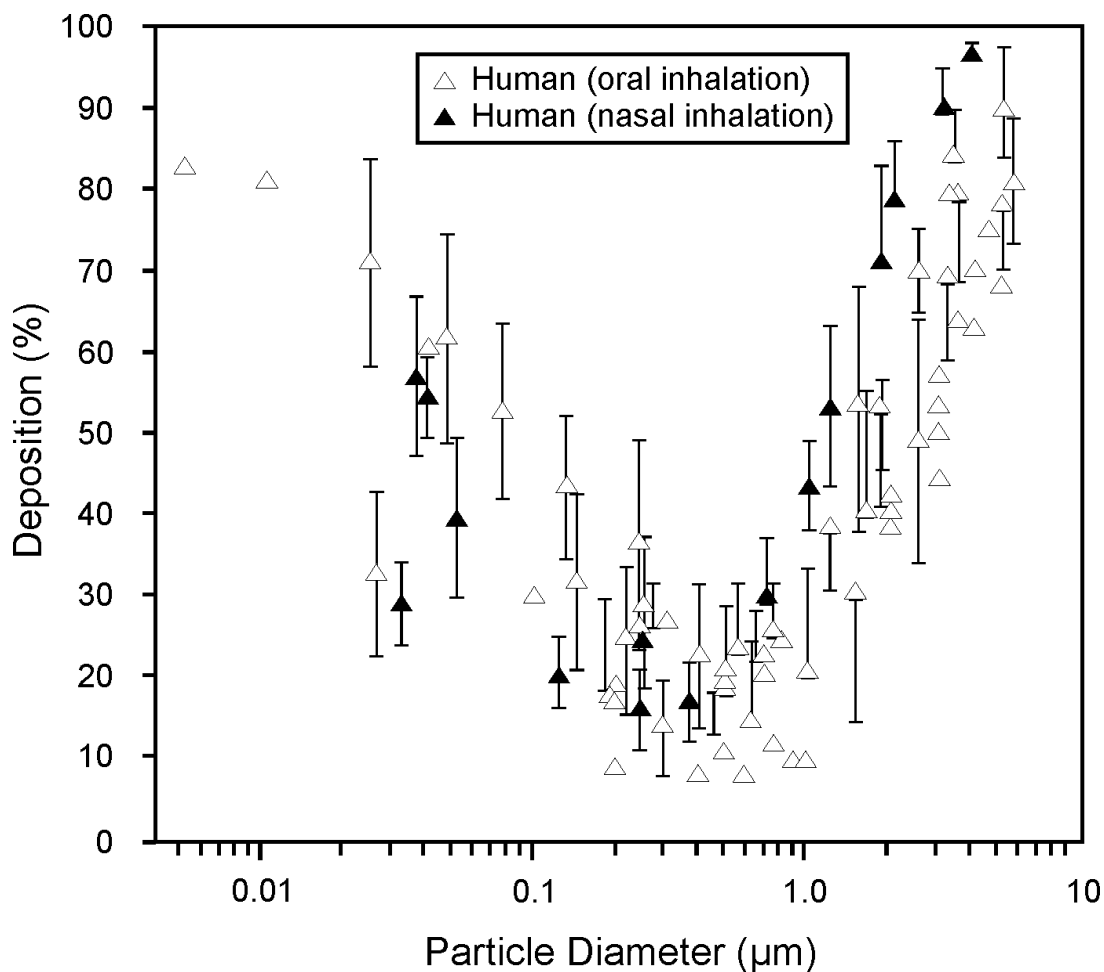
Figure 6-2. Total respiratory tract deposition (as percentage deposition of amount inhaled) in humans as a function of particle size. All values are means with standard deviations when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 μm.

Source: Modified from Schlesinger (1989).

1   particles are deposited. As the particle size decreases from ≈ 0.5 μm, diffusional deposition

2   becomes dominant and total deposition depends more on the actual physical diameter of the

3   particle, with decreasing particle diameter leading to an increase in total deposition. Total

4   deposition shows a minimum for particle diameters in the range of 0.2 to 1.0 μm where, as noted

5   above, neither sedimentation, impaction, or diffusion deposition are very effective.

1   Besides particle size, breathing pattern is the most important factor affecting lung
2   deposition. Kim (2000) reported total lung deposition values in healthy adults for a wide range
3   of breathing patterns, tidal volumes (375 to 1500 mL), flow rates (150 to 1000 mL/s), and
4   respiratory times (2 to 12 s). Total lung deposition increased with increasing tidal volume at a
5   given flow rate and with increasing flow rate at a given respiratory time. Various deposition
6   values were correlated with a single composite parameter consisting of particle size, flow rate,
7   and tidal volume.
8   One of the specific size modes of the ambient aerosol that is being evaluated in terms of
9   potential toxicity is the ultrafine mode (i.e., particles having diameters <0.1 μm). There is,
10   however, little information on total respiratory tract deposition of such particles. Frampton et al.
11   (2000) exposed healthy adult human males and females, via mouthpiece, to 0.0267 μm diameter
12   carbon particles (at 10 μg/m^3) for 2 h at rest. The inspired and expired particle number
13   concentration and size distributions were evaluated. Total respiratory tract deposition fraction
14   was determined for six particle size fractions, ranging from 0.0075 to 0.1334 μm. They found an
15   overall total lung deposition fraction of 0.66 (by particle number) or 0.58 (by particle mass),
16   indicating that exhaled mean particle diameter was slightly larger than inhaled diameter. There
17   was no gender difference. The deposition fraction decreased with increasing particle size within
18   the ultrafine range, from 0.76 at the smallest size to 0.47 at the largest.
19   Jaques and Kim (2000) measured total deposition fraction (TDF) of ultrafine particles
20   [number median diameter (NMD) = 0.04-0.1 μm and σ_g = 1.3] in 22 healthy adults (men and
21   women in equal number) under a variety of breathing conditions. The study was designed to
22   obtain a rigorous data set for ultrafine particles that could be applied to health risk assessment.
23   TDF was measured for six different breathing patterns: tidal volume (V_t) of 500 mL at
24   respiratory flow rates (Q) of 150 and 250 mL/s; V_t = 750 mL at Q of 250 and 375 mL/s; V_t = 1 L
25   at Q of 250 and 500 mL/s. Aerosols were monitored continuously by a modified condensation
26   nuclei counter during mouthpiece inhalation with the prescribed breathing patterns. For a given
27   breathing pattern, TDF increased as particle size decreased, regardless of the breathing pattern
28   used. For example, at V_t = 500 mL and Q = 250 mL/s, TDF was 0.26, 0.30, 0.35, and 0.44 for
29   NMD = 0.10, 0.08, 0.06, and 0.04 μm, respectively (see Figure 6-3). For a given particle size,
30   TDF increased with an increase in V_t and a decrease in Q, indicating an importance of breathing
31   pattern in assessing respiratory dose. The study also found that TDF was greater for women than
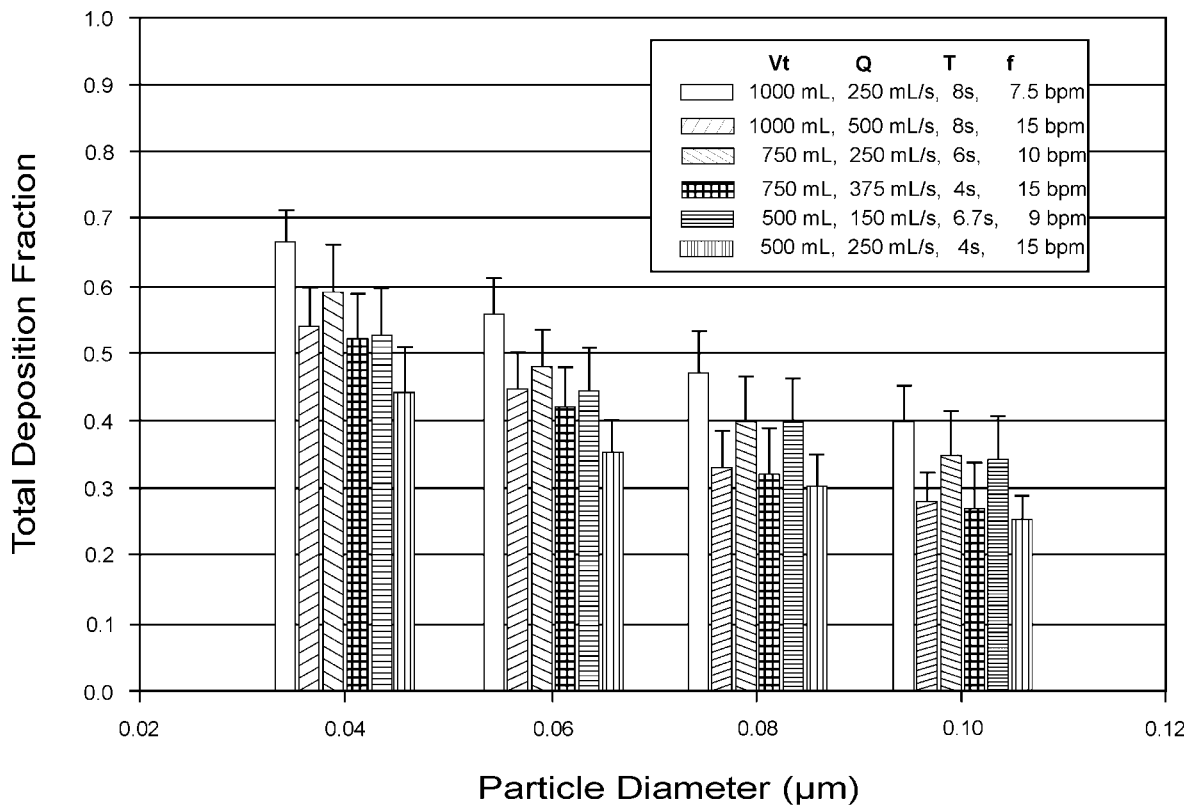
Figure 6-3. Total deposition fraction as a function of particle size in 22 healthy men and women under six different breathing patterns. For each breathing pattern, the total deposition fraction is different (p < 0.05) for two successive particle sizes. V_t is tidal volume (mL); Q is respiratory flow rate (mL/s); T is respiratory time (s); and f is breathing frequency in breaths/min (bpm).

Source: Jacques and Kim (2000).

1   men at NMD = 0.04 μm within all breathing patterns used, but the difference was smaller or

2   negligible for larger sized ultrafine particles. The results clearly demonstrate that the TDF of

3   ultrafine particles increases with a decrease of particle size and with breathing patterns of longer

4   respiratory time, a pattern that is consistent with deposition by diffusion mechanism. The results

5   also suggest that there is a differential lung deposition of very small ultrafine particles for men

6   vs. women. These data are the only systematic human experimental data for ultrafine particles

7   reported since the 1996 PM AQCD.

1   A property of some ambient particulate species that affects deposition is hygroscopicity, the

2   propensity of a material for taking up and retaining moisture under certain conditions of humidity

3   and temperature. Such particles can increase in size in the humid air within the respiratory tract

4   and, when inhaled, will deposit according to their hydrated size rather than their initial size. The

5   implications of hygroscopic growth on deposition have been reviewed extensively by Morrow

6   (1986) and Hiller (1991); whereas the complications of studying lung deposition of hygroscopic

7   aerosols have been reviewed recently by Kim (2000). In general, compared to nonhygroscopic

8   particles of the same initial size, the deposition of hygroscopic aerosols in different regions of the

9   lung may be higher or lower, depending on the initial size. Thus, for particles with initial sizes

10   larger than ≈0.5 μm, the influence of hygroscopicity would be to increase total deposition with a

11   shift from peripheral to central or extrathoracic regions; whereas for smaller ones total deposition

12   would tend to be decreased.

13

14   **6.2.2.2 Deposition in the Extrathoracic Region**

15   The fraction of inhaled particles depositing in the ET region is quite variable, depending on

16   particle size, flow rate, breathing frequency and whether breathing is through the nose or the

17   mouth (Figure 6-4). Mouth breathing bypasses much of the filtration capabilities of the nasal

18   airways, leading to increased deposition in the lungs (TB and A regions). The ET region is

19   clearly the site of first contact with particles in the inhaled air and essentially acts as a "prefilter"

20   for the lungs.

21   Since release of the 1996 PM AQCD, a number of studies have explored ET deposition

22   with in vivo studies, as well as in both physical and mathematical model systems. In one study,

23   the relative distribution of particle deposition between the oral and nasal passages was assessed

24   during "inhalation" by use of a physical model (silicone rubber) of the human upper respiratory

25   system, extending from the nostrils and mouth through the main bronchi (Lennon et al., 1998).

26   Monodisperse particles ranging in size from 0.3 to 2.5 μm were used at various flow rates

27   ranging from 15 to 50 L/min. Total deposition in the model, as was regional deposition in the

28   oral passages, lower oropharynx-trachea, nasal passages, and nasopharynx-trachea, were

29   assessed. Deposition within the nasal passages was found to agree with available data obtained

30   from a human inhalation study (Heyder and Rudolf, 1977), being proportional to particle size,

31   density, and inspiratory flow rate. It also was found that for oral inhalation, the relative
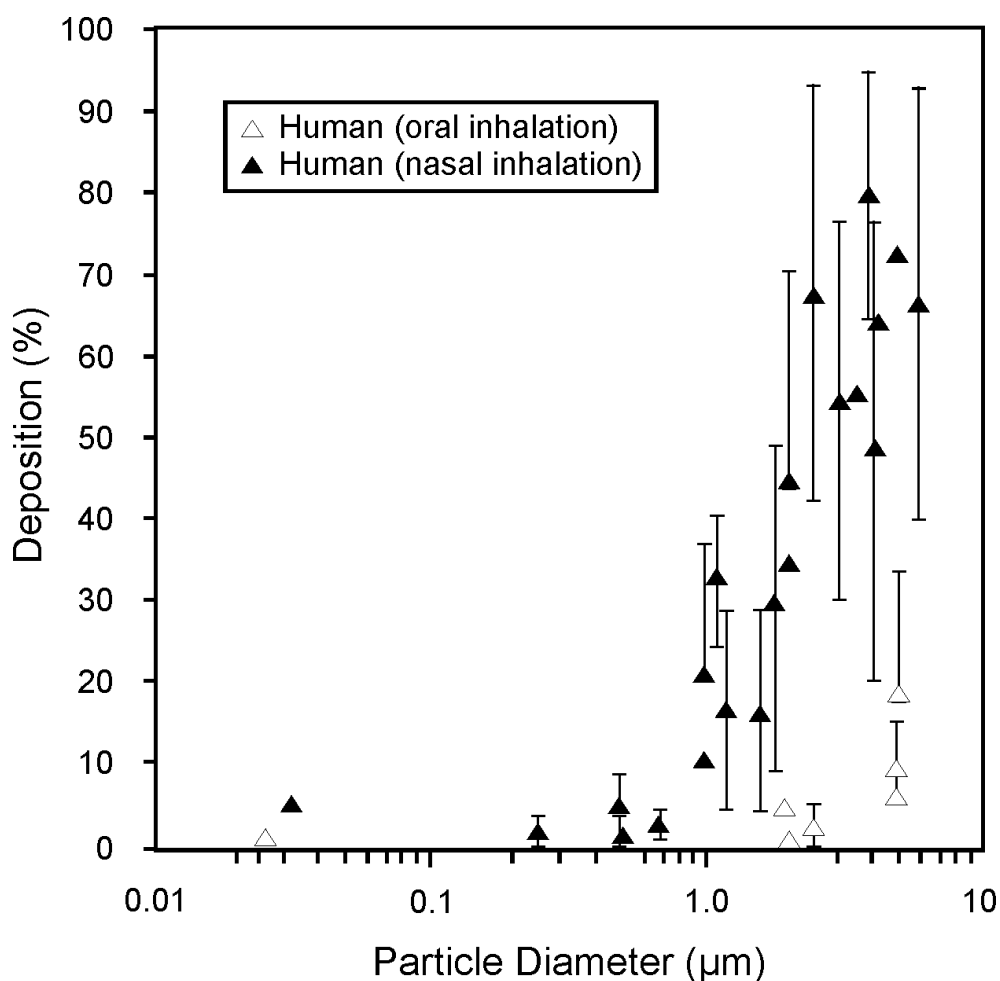
Figure 6-4. **Extrathoracic deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥0.5 μm and geometric (or diffusion equivalent) for those < 0.5 μm.**

Source: Modified from Schlesinger (1989).

1   distribution between the oral cavity and the oropharynx-trachea was similar; whereas for nasal

2   inhalation, the nasal passages contained most of the particles deposited in the model, with only

3   about 10% depositing in the nasopharynx-trachea region. Furthermore, the deposition efficiency

4   of the nasopharynx-trachea region was greater than that of the oropharynx-trachea region.

5   For simulated oronasal breathing, deposition in the ET region depended primarily on particle size

6   rather than flow rate. For all flows and for all breathing modes, total deposition in the ET region

1   increased as particle diameter increased. Such information on deposition patterns in the ET

2   region is useful in refining empirical deposition models.

3   Deposition within the nasal passages was further evaluated by Kesavanathan and Swift

4   (1998), who examined the deposition of 1- to 10-μm particles in the nasal passages of normal

5   adults under an inhalation regime in which the particles were drawn through the nose and out

6   through the mouth at flow rates ranging from 15 to 35 L/min. At any particle size, deposition

7   increased with increasing flow rate; whereas at any flow rate, deposition increased with

8   increasing particle size. In addition, as was shown experimentally by Lennon et al. (1998) under

9   oronasal breathing conditions, deposition of 0.3- to 2.5-μm particles within the nasal passages

10   was significantly greater than within the oral passages, and nasal inhalation resulted in greater

11   total deposition in the model than did oral inhalation. These results are consistent with other

12   studies discussed in the 1996 PM AQCD and with the known dominance of impaction deposition

13   within the ET region.

14   Rasmussen et al. (2000) measured deposition in the nasal cavity of normal adult humans of

15   0.7 μm particles consisting of sodium chloride and radioactively-labeled DTPA. Inspiration

16   occurred under different levels of flow rate ranging from 10-30 L/min. They found that the

17   deposition fraction in the nasal passages increased as flow rate increased and that an estimate of

18   maximum linear air velocity was the best single predictor of nasal deposition fraction.

19   For ultrafine particles ($d_p < 0.1$ μm), deposition in the ET region is controlled by diffusion,

20   which depends only on the particle's geometric diameter. Prior to 1996, ET deposition for this

21   particle size range had not been studied extensively in humans, and this remains the case. In the

22   earlier 1996 PM AQCD, the only data available for ET deposition of ultrafine particles were

23   from cast studies. More recently, deposition in the ET region was examined using mathematical

24   modeling. Three dimensional numerical simulations of flow and particle diffusion in the human

25   upper respiratory tract, which included the nasal region, oral region, larynx, and first two

26   generations of bronchi, were performed by Yu et al. (1998). Deposition of particles of 0.001 and

27   0.1 μm in these different regions was calculated under inspiratory and expiratory flow conditions.

28   Deposition efficiencies in the total model were lower on expiration than inspiration although

29   values for the former were quite high. Nasal deposition of ultrafine particles can also be quite

30   high. For example, nasal deposition accounted for up to 54% of total deposition in the model

31   system for 0.001-μm particles. The total deposition efficiency in the model was 75% (of the

1   amount entering) for this size particle. With oral breathing, deposition efficiency was estimated

2   at 48% (of amount entering) (Yu et al., 1998).

3   Swift and Strong (1996) examined the deposition of ultrafine particles, ranging in size from

4   0.053 to 0.062 μm, in the nasal passages of normal adults during constant inspiratory flows of

5   6 to 22 L/min. The results are consistent with results noted in studies above, namely that the

6   nasal passages are highly efficient collectors for ultrafine particles. In this case, fractional

7   deposition ranged from 94 to 99% (of amount inhaled). There was found to be only a weak

8   dependence of deposition on flow rate, which contrasts with results noted above (i.e., Lennon

9   et al., 1998) for particles >0.3 μm, but is consistent with diffusion as the main deposition

10 mechanism.

11   Cheng et al. (1997) examined oral airway deposition in a replicate cast of the human nasal

12 cavity, oral cavity, and laryngeal-tracheal sections. Particle sizes ranged from 0.005 to 0.150 μm,

13 and constant inspiratory and expiratory flow rates of 7.5 to 30 L/min were used. They noted that

14 the deposition fractions within the oral cavity were essentially the same as that in the

15 laryngeal-tracheal sections for all particle sizes and flow rates. They ascribed this to the balance

16 between flow turbulence and residence time in these two regions. Svartengren et al. (1995)

17 examined the effect of changes in external resistance on oropharyngeal deposition of 3.6-μm

18 particles in asthmatics. Under controlled mouthpiece breathing conditions (flow rate 0.5 L/s), the

19 median deposition as a percentage of inhaled particles in the mouth and throat was 20%

20 (mean = 33%; range 12 to 84%). Although the mean deposition fell to 22% with added

21 resistance, the median value remained at 20% (range 13 to 47%). Fiberoptic examination of the

22 larynx revealed that there was a trend for increased mouth and throat deposition associated with

23 laryngeal narrowing. Katz et al. (1999) indicate, on the basis of mathematical model

24 calculations, that turbulence plays a key role in enhancing particle deposition in the larynx and

25 trachea.

26   The results of all of the above studies support the previously known ability of the ET

27 region, and especially the nasal passages, to act as an efficient filter for nanoparticles (<0.1 μm)

28 as well as for larger ones (>5μm), potentially reducing the amount of particles within a wide size

29 range that are available for deposition in the TB and A regions.

30

31

6.2.2.3 Deposition in the Tracheobronchial and Alveolar Regions

Particles that do not deposit in the ET region of the respiratory tract enter the lungs; however, their regional deposition within the lungs cannot be precisely measured. Much of the available deposition data for the TB and A regions have been obtained from experiments with radioactively labeled, poorly soluble particles (Figures 6-5 and 6-6, respectively). These have been described previously (U.S. Environmental Protection Agency, 1996). Although there are no new regional data obtained by means of the radioactive aerosol method since the publication of that document, a novel serial bolus delivery method has been introduced. Using this bolus technique, regional deposition has been measured for fine and coarse aerosols (Kim et al., 1996; Kim and Hu, 1998) and for ultrafine aerosols (Kim and Jacques, 2000). The serial bolus method uses nonradioactive aerosols and can measure regional deposition in a virtually unlimited number of lung compartments. Because of experimental limitations of the technique, the investigators measured regional lung deposition in ten serial, 50 mL increments from the mouth to the end of a typical 500 mL tidal volume. Deposition measurements in the TB and A regions were obtained for both men and women for particles ranging from 0.04 to 5.0 μm in diameter. It should be noted that particle deposition in the TB and A regions was based on volumetric compartments of 50 to 150 mL and >150 mL, respectively. Deposition in the ET region was based on the 0 to 50 mL compartment. Lung deposition fractions in the TB and A regions obtained by the bolus technique are shown in Figure 6-7. Of total particle deposition in the lung, 23 to 32% was deposited in the TB region and 68 to 77% was deposited in the A region. Deposition in women was consistently greater in the TB region by 21 to 47%, but was comparable or slightly smaller in the A region when compared to men. As a result, total lung deposition was slightly greater in women than men ($\approx$5 to 15%).

6.2.2.4 Local Distribution of Deposition

Airway structure and its associated air flow patterns are exceedingly complex, and ventilation distribution of air in different parts of the lung is uneven. Thus, it is expected that particle deposition patterns within the ET, TB, and A regions would be highly nonuniform, with some sites exhibiting deposition that is much greater than average levels within these regions. This was discussed in detail previously in the 1996 PM AQCD. Basically, using deposition data from living subjects as well as from mathematical and physical models, enhanced deposition has
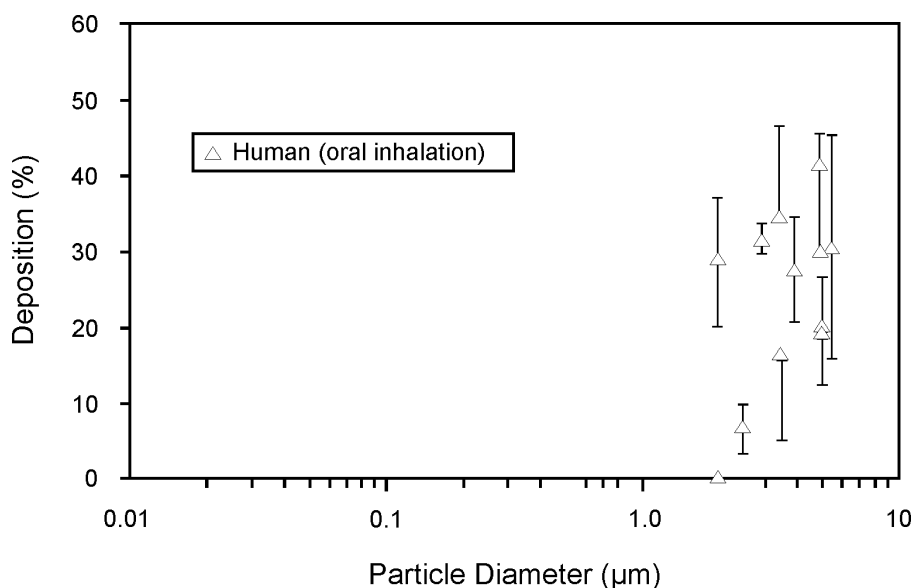
Figure 6-5. **Tracheobronchial deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥0.05 μm and geometric (or diffusion equivalent) for those < 0.5 μm.**

Source: Modified from Schlesinger (1989).
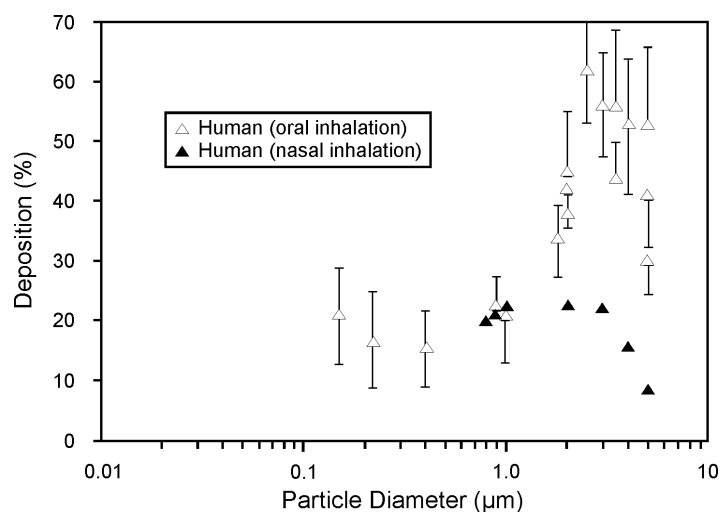
Figure 6-6. Alveolar deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥0.05 μm and geometric (or diffusion equivalent) for those < 0.5 μm.

Source: Modified from Schlesinger (1989).
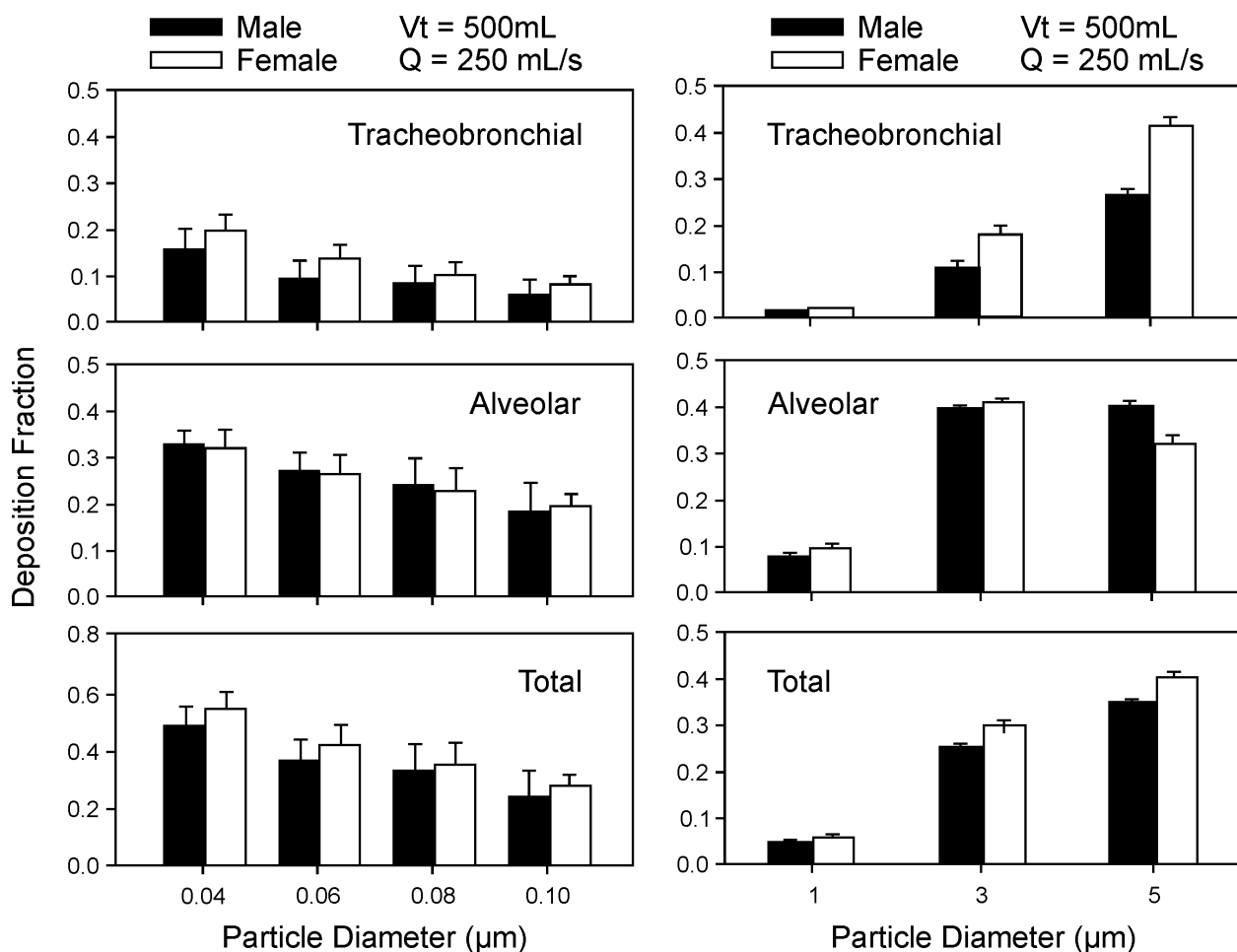
Figure 6-7. **Lung deposition fractions in the tracheobronchial (TB) and alveolar (A) regions obtained by the bolus technique. Using a breathing pattern of 500 mL at 15 breaths per min, TB deposition was 1.5, 10.6, and 26.1% and A deposition was 7.7, 39.4, and 39.8% for particles of 1, 3, and 5 μm in diameter, respectively, for men. In comparison to men, TB deposition in women was 26 to 53% greater, whereas A deposition was comparable. For ultrafine particles of 0.04 to 0.1 μm diameter, TB and A deposition ranged from 5.7 to 15.6% and 18.2 to 33.1%, respectively. Both TB and A deposition decreased with increasing particle size within the ultrafine range, which is consistent with deposition theory.**

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

1   been shown to occur in the nasal passages and trachea and at branching points in the TB and

2   A regions (see Chapter 10 of U.S. Environmental Protection Agency, 1996). Churg and Vedal

1   (1996) examined retention of particles on carinal ridges and tubular sections of airways from

2   lungs obtained at necropsy. Results indicated significant enhancement of particle retention on

3   carinal ridges through the segmental bronchi; the ratios were similar in all airway generations

4   examined.

5   Kim and Fisher (1999) studied local deposition efficiencies and deposition patterns of

6   aerosol particles (2.9 to 6.7 μm) in sequential double bifurcation tube models with two different

7   branching geometries: one with in-plane (A) and another with out of plane (B) bifurcation. The

8   deposition efficiencies (DE) in each bifurcation increased with increasing Stokes number (Stk).

9   With symmetric flow conditions, DE was somewhat smaller in the second than the first

10 bifurcation in both models. DE was greater in the second bifurcation in model B than in model

11 A. With asymmetric flows, DE was greater in the low-flow side compared to the high-flow side;

12 and this was consistent in both models. Deposition pattern analysis showed highly localized

13 deposition on and in the immediate vicinity of each bifurcation ridge, regardless of branching and

14 flow patterns.

15   Comer et al. (2000) used a three-dimensional computer simulation technique to investigate

16 local deposition patterns in sequentially bifurcating airway models that were previously used in

17 experiments by Kim and Fisher (1999). The simulation was for 3-, 5-, and 7-μm particles and

18 assumed steady, laminar, constant air flow with symmetry about the first bifurcation. The overall

19 trend of the particle deposition efficiency, i.e., an exponential increase with Stokes number, was

20 similar for all bifurcations, and deposition efficiencies in the bifurcation regions agreed very well

21 with experimental data. Local deposition patterns consistently showed that the majority of the

22 deposition occurred within the carinal region.

23   Deposition "hot spots" at airway bifurcations have undergone additional analyses using

24 mathematical modeling techniques. Using calculated deposition sites, a strong correlation has

25 been demonstrated between secondary flow patterns and deposition sites and density both for

26 large (10 μm) particles and for ultrafine particles (0.01 μm) (Heistracher and Hofmann, 1997;

27 Hofmann et al., 1996). This supports experimental work, noted in U.S. Environmental

28 Protection Agency (1996), indicating that, like larger particles, ultrafine particles also show

29 enhanced deposition at airway branch points — even in the upper tracheobronchial tree.

30   The pattern of particle distribution on a more regional scale was evaluated by Kim et al.

31 (1996) and Kim and Hu (1998). Deposition patterns were measured in situ in nonsmoking

1   healthy young adult males using, an aerosol bolus technique that delivered 1-, 3-, or 5-μm

2   particles into specific volumetric depths within the lungs. The distribution of particle deposition

3   was uneven; and it was noted that sites of peak deposition shifted from distal to proximal regions

4   of the lungs with increasing particle size (Figure 6-8). Furthermore, the surface dose was found

5   to be greater in the conducting airways than in the alveolar region for all of the particle sizes

6   evaluated. Within the conducting airways, the largest airway regions (i.e., 50 to 100 mL volume

7   distal to the larynx) received the greatest surface doses.

8   Kim and Jaques (2000) used the respiratory bolus technique to measure the deposition

9   distribution of ultrafine particles (0.04, 0.06, 0.08, and 0.1 μm) in young adults. Under normal

10   breathing conditions (tidal volume 500 mL, respiratory flow rate 250 mL/s), bolus aerosols were

11   delivered sequentially to a lung depth ranging from 50 to 500 mL in 50-mL increments. The

12   results indicate that regional deposition varies widely along the depth of the lung, regardless of

13   particle size (Figure 6-8). The deposition patterns for ultrafine particles, especially for very small

14   ultrafine particles, were similar to those for coarse particles. Peak deposition occurred in the

15   lung regions situated between 150 and 200 mL from the mouth, and sites of peak deposition

16   shifted proximally with a decrease in particle size. Deposition dose per unit average surface area

17   was greatest in the proximal lung regions and decreased rapidly with increased lung depth. Peak

18   surface dose was 5 to 7 times greater than average lung dose. These results indicate that local

19   enhancement of dose occurs in healthy lungs, which could be an important factor in eliciting

20   pathophysiological effects.

21

22   **6.2.2.5 Deposition of Specific Size Modes of Ambient Aerosol**

23   The studies described in previous sections generally evaluated deposition using individual

24   particle sizes within certain ranges without consideration of specific relevant ambient size ranges.

25   Some recent modeling studies, however, have considered the deposition profiles of particle

26   modes that exist in ambient air, so as to provide estimates on dosimetry of these "real world"

27   particle size fractions. One such study using a lung-anatomical model (Venkataraman and Kao,

28   1999) examined the contribution of two specific size modes of the PM_{10} ambient aerosol, namely

29   the fine mode (defined as particles with diameters up to 2.5 μm) and the thoracic fraction of the

30   coarse mode (defined as particles with diameters 2.5 to 10 μm), to total lung and regional lung

31   doses (i.e., a daily dose expressed as μg/day, and a surface dose expressed a μg/cm^2/day)
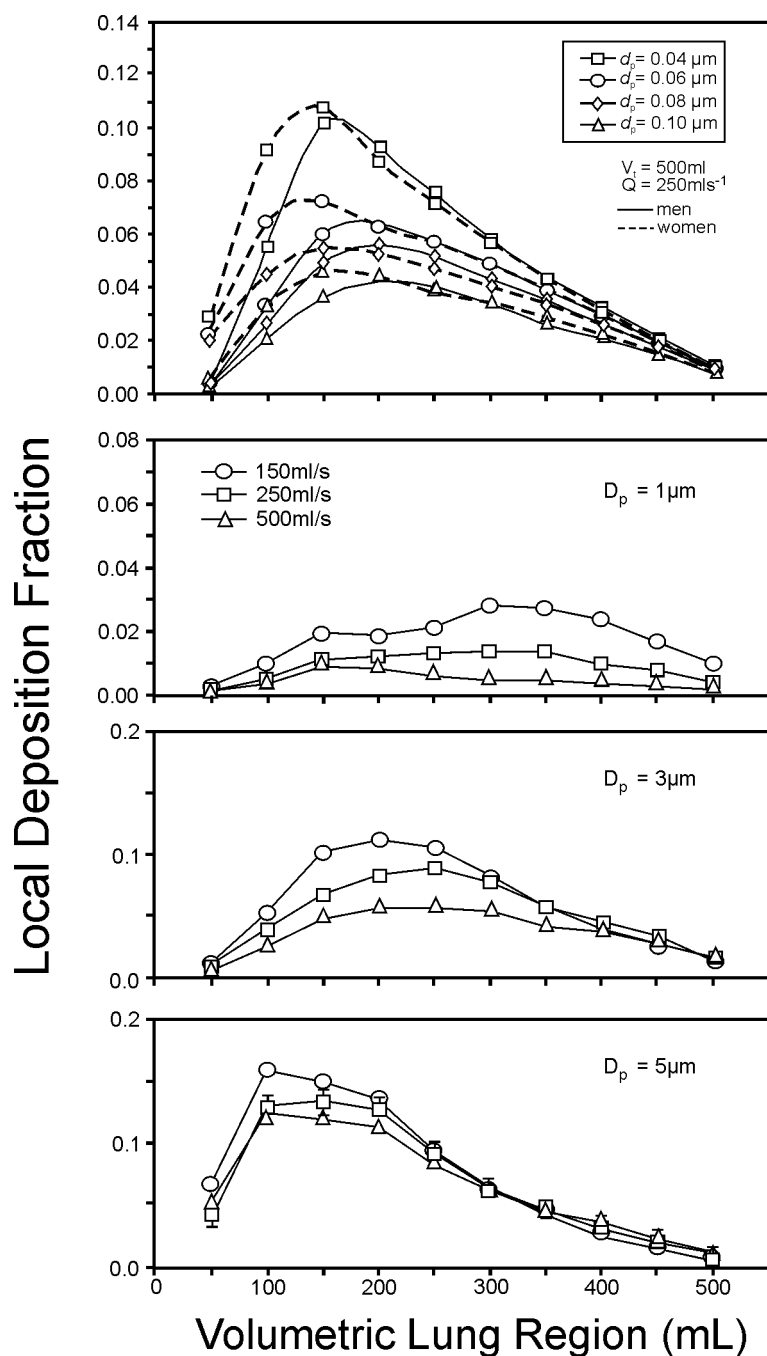
Figure 6-8. Lung deposition fractions in ten volumetric regions for particle sizes ranging from ultrafine particle diameter (d_p) of 0.04 to 0.01 μm (Panel A) to fine (d_p = 1.0 μm) (Panel B) and coarse (d_p = 3 and 5 μm) (Panels C and D). Healthy young adults inhaled a small bolus of monodisperse aerosols under a range of normal breathing conditions (ie., tidal volume of 500 mL at breathing frequencies of 9, 15, and 30 breaths per min.).

Source: Kim et al. (1996); Kim and Hu (1998); Kim and Jacques (2000).

1   resulting from a 24-h exposure to a particle concentration of 150 μg/m^3. The study also

2   evaluated deposition in terms of two metrics, namely mass dose and number dose. Deposition

3   was calculated using a mathematical model for a healthy human lung under both simulated

4   moderate exertion (1 L at 15 breaths/min) and vigorous exertion (1.5 L at 15 breaths/min), and

5   for a compromised lung (0.5 L at 30 breaths/min). Regional deposition values were obtained for

6   the ET, TB, and A regions. Because the exposure scenario used is quite unrealistic, only general

7   trends should be inferred from this study rather than actual deposition values.

8   Daily mass dose peaked in the A airways for all breathing patterns; whereas that for the

9   coarse fractions was comparable in the TB and A regions. The mass per unit surface area of

10   various airways from the fine and coarse fractions was larger in the trachea and first few

11   generations of bronchi. It was suggested that these large surface doses may be related to

12   aggravation of upper respiratory tract illness in geographical areas where coarse particles are

13   present.

14   The daily number dose was different for fine and coarse fractions in all lung airways, with

15   the dose from the fine fraction higher by about 100 times in the ET and about 10^5 times in

16   internal lung airways. The surface number dose (particles/cm^2/day) was 10^3 to 10^5 times higher

17   for fine than for coarse particles in all lung airways, indicating the larger number of fine particles

18   depositing. Particle number doses did not follow trends in mass doses and are much higher for

19   fine than coarse particles and are higher for different breathing patterns. It also was concluded

20   that the fine fraction contributes 10,000 times greater particle number per alveolar macrophage

21   than the coarse fraction particles. As noted, these results must be viewed with caution because

22   they were obtained using a pure mathematical model that must be validated in terms of realistic

23   physiologic conditions.

24   Another evaluation of deposition that included consideration of size mode of the ambient

25   aerosol was that of Broday and Georgopoulos (2001). In this case, a mathematical model was

26   used to account for particle hygroscopic growth, transport, and deposition in tracking the changes

27   in the size distribution of inhaled aerosols. It was concluded that different rates of particle

28   growth in the inspired air resulted in a change in the aerosol size distribution, such that increased

29   mass and number fractions of inspired ultrafine particles (< 0.1 μm) were found in the size range

30   between 0.1 to 1 μm and, therefore, deposited to a lesser extent due to a decrease in diffusion

31   deposition. On the other hand, particles that were originally in the 0.1 to 1 μm size range when

1   inhaled will undergo enhanced deposition because of their increase in size resulting from

2   hygroscopic growth. Hence, the initial size distribution of the inhaled polydisperse aerosol

3   affects the evolution of size distribution once inhaled and, thus, its deposition profile in the

4   respiratory tract. Hygroscopicity of respirable particles must be considered for accurate

5   predictions of deposition. Because different size fractions likely have different chemical

6   composition, such changes in deposition patterns will affect biological responses.

7

8   ## 6.2.3 Biological Factors Modulating Deposition

9   Experimental deposition data in humans are commonly derived using healthy adult

10   Caucasian males. Various factors can act to alter deposition patterns from those obtained in this

11   group. Evaluation of these factors is important to help understand potentially susceptible

12   subpopulations because differences in biological response following pollutant exposure may be

13   caused by dosimetry differences as well as by differences in innate sensitivity. The effects of

14   different biological factors on deposition were discussed in the 1996 PM AQCD (U.S.

15   Environmental Protection Agency, 1996) and are summarized below together with additional

16   information obtained from more recent studies.

17

18   **6.2.3.1 Gender**

19   Males and females have different body size and ventilatory parameter distributions;

20   therefore, it is expected that there would be gender differences in deposition. In some of the

21   controlled studies, however, men and women are breathing at the same tidal volume and

22   frequency. If the women are generally smaller than the men, the increased minute ventilation

23   compared to their normal ventilation would cause different changes in deposition patterns.

24   In these cases, it would be better for the investigators to have used size-adjusted tidal volumes.

25   This may help to explain some of the differing results discussed below.

26   Using particles in the 2.5- to 7.5-μm size range, Pritchard et al. (1986) indicated that, for

27   comparable particle sizes and inspiratory flow rates, females had higher ET and TB deposition

28   and smaller A deposition than did males. The ratio of A deposition to total thoracic deposition in

29   females also was found to be smaller. These differences were attributed to gender differences in

30   airway size.

1   In another study (Bennett et al., 1996), the total respiratory tract deposition of 2-μm

2   particles was examined in adult males and females aged 18 to 80 years who breathed with a

3   normal resting pattern. Deposition was assessed in terms of a deposition fraction, which was the

4   difference between the amount of particles inhaled and exhaled during oral breathing. Although

5   there was a tendency for a greater deposition fraction in females compared to males, and because

6   males had greater minute ventilation, the deposition rate (i.e., deposition per unit time) was

7   greater in males than in females.

8   Kim and Hu (1998) assessed regional deposition patterns in healthy adult males and

9   females using particles with median aerodynamic sizes of 1, 3, and 5 μm and a bolus delivery

10   technique that involved controlled breathing. The total deposition in the lungs was similar for

11   both genders with the smallest particle, but was greater in women for the 3- and 5-μm particles,

12   regardless of the inhalation flow rate used; this difference ranged from 9 to 31%, with higher

13   values associated with higher flow rates. The pattern of deposition was similar for both genders

14   although females showed enhanced deposition peaks for all three particle sizes. The volumetric

15   depth location of these peaks was found to shift from peripheral (i.e., increased volumetric depth)

16   to proximal (i.e., shallow volumetric depth) regions of the lung with increasing particle size, but

17   the shift was greater in females than in males. Thus, deposition appeared to be more localized in

18   the lungs of females compared to those of males. These differences were attributed to a smaller

19   size of the upper airways in females than in males, particularly of the laryngeal structure. Local

20   deposition of 1-μm particles was somewhat flow dependent but, for larger (5-μm) particles, was

21   largely independent of flow (flows did not include those that would be typical of exercise).

22   In a related study, Kim et al. (2000) evaluated differences in deposition between males and

23   females in terms of exercise levels of ventilation and breathing patterns. Using particles at the

24   same size noted above and a number of breathing conditions, total lung deposition was

25   comparable between men and women for l-μm particles, but was slightly greater in women than

26   men for 3- and 5-μm particles with all breathing patterns. The gender difference was about 15%

27   at rest, and variable during exercise, depending on particle size. However, total lung deposition

28   rate (i.e., deposition per unit time) was found to be 3 to 4 times greater during moderate exercise

29   than during rest for all particle sizes. Thus, it was concluded that exercise may increase the

30   health risk from particles because of increased large airway deposition and that women may be

31   more susceptible to this exercise-induced change.

1   Jaques and Kim (2000) and Kim and Jaques (2000) expanded the evaluation of deposition

2   in males and females to particles <1 μm. They measured total lung deposition in healthy adults

3   using sizes in the ultrafine mode (0.04 to 0.1 μm), in addition to those having diameters of 1 and

4   5 μm. Total lung deposition was greater in females than in males for 0.04- and 0.06-μm

5   particles. The difference was negligible for 0.08- and 0.1-μm particles. Therefore, the gender

6   effect was particle-size dependent, showing a greater deposition in females for very small

7   ultrafine and large coarse particles, but not for particles ranging from 0.08 to 1 μm. A local

8   deposition fraction was determined in each volumetric compartment of the lung to which

9   particles are injected based on the inhalation procedure (Kim and Jaques, 2000). The deposition

10   fraction was found to increase with increasing lung depth from the mouth, reach a peak value,

11   and then decrease with further increase in lung volumetric depth. The height of the peak and its

12   depth did vary with particle size and breathing pattern. Peak deposition for the 5-μm particles

13   was more proximal than that for the 1-μm particles; whereas that for the ultrafine particles

14   occurred between these two peaks. For the ultrafine particles, the peak deposition became more

15   proximal as particle size decreased. Although this pattern of deposition distribution was similar

16   for both men and women, the region of peak deposition was shifted closer to the mouth and peak

17   height was slightly greater for women than for men for all exposure conditions.

18

19   **6.2.3.2 Age**

20   Airway structure and respiratory conditions vary with age, and these variations may alter

21   the deposition pattern of inhaled particles. The limited experimental studies reported in the 1996

22   PM AQCD (U. S. Environmental Protection Agency, 1996) indicated results ranging from no

23   clear dependence of total deposition on age to slightly higher deposition in children than adults.

24   However, children have a different resting ventilation than do adults. The experimental studies

25   must adjust for the higher minute ventilation per unit body weight in children when comparing

26   deposition results to those obtained in adults.

27   Potential regional deposition differences between children and adults have been assessed to

28   a greater extent using mathematical models. These indicated that, if the entire respiratory tract

29   and a complete breathing cycle at normal rate are considered, then ET deposition in children

30   would be generally higher than that in adults, but TB and A regional deposition in children may

31   be either higher or lower than that in adults, depending on particle size (Xu and Yu, 1986).

1   Enhanced deposition in the TB region would occur for particles <5 μm in children (Xu and Yu,

2   1986; Hofmann et al., 1989a).

3   An age dependent theoretical model to predict regional particle deposition in childrens'

4   lungs that incorporates breathing parameters and morphology of the growing lung was developed

5   by Musante and Martonen (1999). The model was used to compare deposition of monodisperse

6   aerosols, ranging from 0.25 to 5 μm, in the lungs of children (aged 7, 22, 48, and 98 mo) at rest

7   to that in adults (aged 30 years) at rest. Compared to adults, A deposition was highest in the

8   48- and 98-mo subjects for all particle sizes; TB deposition was found to be a monotonically

9   decreasing function of age for all sizes; and total lung deposition (i.e., TB+A) was generally

10   higher in children than adults, with children of all ages showing similar total deposition fractions.

11   This model was used by Musante and Martonen (2000a) to evaluate the deposition of a

12   polydisperse aerosol that has been extensively used in toxicological studies, namely residual oil

13   fly ash (ROFA) having an MMAD of 1.95 μm, a geometric standard deviation of 2.19, and a

14   CMD of 0.53 (assuming a particle density of 0.34 g/cm^2). Deposition was evaluated under

15   resting breathing conditions. The mass based deposition fraction of the particles was found to

16   decrease with age from 7 mo to adulthood, but the mass deposition per unit surface area in the

17   lungs of children could be significantly greater than that in the adult.

18   Phalen and Oldham (2001) calculated the respiratory deposition of particles with sizes

19   ranging from 0.1 to 10 μm in diameter for 20 year-old adults and 2 year-old children. Total lung

20   deposition was comparable between adults and children for all particle sizes tested; however, TB

21   deposition was much greater in children than in adults (from 13 to 81%, depending on particle

22   size). Particle deposition in the A region was significantly reduced in children.

23   Cheng et al. (1995) examined deposition of ultrafine particles in replica casts of the nasal

24   airways of children aged 1.5 to 4 years. Particle sizes ranged from 0.0046 to 0.2 μm, and both

25   inspiratory and expiratory flow rates were used (3 to 16 L/min). Deposition efficiency was found

26   to decrease with increasing age for a given particle size and flow rate.

27   Oldham et al. (1997) examined the deposition of monodisperse particles having diameters

28   of 1, 5, 10, and 15 μm in hollow airway models that were designed to represent the trachea and

29   the first few bronchial airway generations of an adult, a 7-year-old child, and a 4-year-old child.

30   They noted that, in most cases, the total deposition efficiency was greater in the child-size

31   models than in the adult model.

1   Bennett et al. (1997a) analyzed the regional deposition of poorly soluble 4.5 μm particles
2   inhaled via mouthpiece. The subjects were children and adults with mild cystic fibrosis (CF), but
3   who likely had normal upper airway anatomy such that intra- and extrathoracic deposition would
4   be similar to that in healthy people. The mean age of the children was 13.8 years and for the
5   adults was 29.1 years. Extrathoracic deposition, as a percentage of total respiratory tract
6   deposition, was higher by about 50% in children compared to adults (30.7%, 20.1%, and 16.0%,
7   respectively). There was an age dependence of ET deposition in the children, in that the
8   percentage ET deposition tended to be higher at a younger age (p = 0.08); the younger group
9   (<14 years) (p = 0.05) had almost twice the percentage ET deposition of the older group
10   (>14 years). Additional analyses showed an inverse correlation of extrathoracic deposition with
11   body height. There was no significant difference in lung or total respiratory tract deposition
12   between the children and adults. Because ET deposition was age dependent, and total deposition
13   was not, this suggests that the ET region does a more effective job in children of filtering out
14   particles that would otherwise reach the TB region. However, because the lungs of children are
15   smaller than are those of adults, children may still have comparable deposition per unit surface
16   area as adults.
17   Bennett and Zeman (1998) measured the deposition of monodisperse 2 μm (MMAD)
18   particles in children (aged 7 to 14 years) and adolescents (aged 14 to 18 years) for comparison to
19   that in adults (19 to 35 years). Each subject inhaled the particles by following their previously
20   determined individual spontaneous resting breathing pattern. Deposition was assessed by
21   measuring the amount of particles inhaled and exhaled. There was no age-related difference in
22   deposition within the children group. There was also no significant difference in deposition
23   between the children and adolescents, between the children and adults, or between the
24   adolescents and adults. However, the investigators noted that, because the children had smaller
25   lungs and higher minute volumes relative to lung size, they likely would receive greater doses of
26   particles per lung surface area compared to adults. Furthermore, breath-to-breath fractional
27   deposition in children did vary with tidal volume, increasing with increasing volume. The rate of
28   deposition normalized to lung surface area tended (p = 0.07) to be greater (35%) in children
29   when compared to the combined group of adolescents and adults. These additional studies still
30   do not provide unequivocal evidence for significant differences in deposition between adults and
31   children, even when considering differences in lung surface area. However, it should be noted

1   that differences in levels of activity between adults and children are likely to play a fairly large

2   role in age-related differences in deposition patterns of ambient particles. Children generally

3   have higher activity levels during the day and higher associated minute ventilation per lung size,

4   which can contribute to a greater size-specific dose of particles. Activity levels in relationship to

5   exposure are discussed more fully in Chapter 5.

6   Another subpopulation of potential concern related to susceptibility to inhaled particles is

7   the elderly. In the study of Bennett et al. (1996), in which the total respiratory tract deposition of

8   2-μm particles was examined in people aged 18 to 80 years, the deposition fraction in the lungs

9   of people with normal lung function was found to be independent of age, depending solely on

10 breathing pattern and airway resistance.

11

12 **6.2.3.3 Respiratory Tract Disease**

13   The presence of respiratory tract disease can affect airway structure and ventilatory

14 parameters, thus altering deposition compared to that occurring in healthy individuals. The effect

15 of airway diseases on deposition has been studied extensively, as described in the 1996 PM

16 AQCD (U.S. Environmental Protection Agency, 1996). Studies described therein had shown that

17 people with chronic obstructive pulmonary disease (COPD) had very heterogeneous deposition

18 patterns, and differences in regional deposition compared to normals. People with asthma and

19 obstructive pulmonary disease tended to have greater TB deposition than did healthy people.

20 Furthermore, there tended to be an inverse relationship between bronchoconstriction and the

21 extent of deposition in the A region; whereas total respiratory tract deposition generally increased

22 with increasing degrees of airway obstruction. The described studies were performed during

23 controlled breathing; i.e., all subjects breathed with the same tidal volume and respiratory rate.

24 However, although resting tidal volume is similar or elevated in people with COPD compared to

25 normal, healthy individuals the former tend to breathe at a faster rate, resulting in higher than

26 normal tidal peak flow and resting minute ventilation. Thus, some of the reported differences in

27 the deposition of particles could have been caused by increased fractional deposition with each

28 breath. Although the extent to which lung deposition may change with respect to particle size,

29 breathing pattern, and disease status in people with COPD is still unclear, some recent studies

30 have attempted to provide additional insight into this issue.

1   Bennett et al. (1997b) measured the fractional deposition of insoluble 2-μm particles in

2   people with severe to moderate COPD (mix of emphysema and chronic bronchitis, mean age

3   62 years) and compared this to healthy older adults (mean age 67 years) under conditions where

4   the subjects breathed using their individual resting breathing pattern, as well as a controlled

5   breathing pattern. People with COPD tended to breathe with elevated tidal volume and at a

6   faster rate than people with healthy lungs, resulting in about 50% higher resting minute

7   ventilation. Total respiratory tract deposition was assessed in terms of deposition fraction, a

8   measure of the amount deposited based on measures of amount of aerosol inhaled and exhaled,

9   and deposition rate, the particles deposited per unit time. Under typical breathing conditions,

10   people with COPD had about 50% greater deposition fraction than did age-matched healthy

11   adults. Because of the elevation in minute ventilation, people with COPD had average

12   deposition rates about 2.5 times that of healthy adults. Similar to previously reviewed studies

13   (U.S. Environmental Protection Agency, 1996), these investigators observed an increase in

14   deposition with an increase in airway resistance, suggesting that, at rest, COPD resulted in

15   increased deposition of fine particles in proportion to the severity of airway disease. The

16   investigators also reported a decrease in deposition with increasing mean effective airspace

17   diameter; this suggested that the enhanced deposition was associated more with the chronic

18   bronchitic component of COPD than with the emphysematous component. Greater deposition

19   was noted with natural breathing compared to the fixed pattern.

20   Kim and Kang (1997) measured lung deposition of 1-μm particles inhaled via the mouth by

21   healthy adults (mean age 27 years) and by those with various degrees of airway obstruction,

22   namely smokers (mean age 27 years), smokers with small airway disease (SAD; mean age

23   37 years), asthmatics (mean age 48 years), and patients with COPD (mean age 61 years)

24   breathing under the same controlled pattern. Deposition fraction was obtained by measuring the

25   number of particles inhaled and exhaled, breath by breath. There was a marked increase in

26   deposition in people with COPD. Deposition was 16%, 49%, 59%, and 103% greater in

27   smokers, smokers with SAD, asthmatics and people with COPD, respectively, than in healthy

28   adults. Deposition in COPD patients was significantly greater than that associated with either

29   SAD or asthma; there was no significant difference in deposition between people with SAD and

30   asthma. Deposition fraction was found to be correlated with percent predicted forced expiratory

31   volume (FEV_1) and forced expiratory flow (FEF25-75%). Airway resistance was not correlated

1   strongly with total lung deposition. Kohlhäufl et al. (1999) showed increased deposition of fine

2   particles (0.9 μm) in women with bronchial hyperresponsiveness.

3   Segal et al. (2000a) developed a mathematical model for airflow and particle motion in the

4   lung that was used to evaluate how lung cancer affects deposition patterns in the lungs of

5   children. It was noted that the presence of airway tumors could affect deposition by increasing

6   probability of inertial deposition and diffusion. The former would occur on upstream surfaces of

7   tumors and the latter on downstream surfaces. It was concluded that particle deposition is

8   affected by the presence of airway disease, that effects may be systematic and could be predicted,

9   and that, therefore, they could be incorporated into dosimetry models.

10   Brown et al. (2001) examined the relationship between regional lung deposition for coarse

11   particles (5 μm) and ventilation patterns in healthy adults and in patients with cystic fibrosis

12   (CF). They found that deposition in the TB region was positively associated with regional

13   ventilation in healthy subjects, but negatively associated in CF patients. The relationships were

14   reversed for deposition in the A region. These data suggest that significant coarse particle

15   deposition may occur in the TB region of poorly ventilated lungs, as occurs in CF; whereas TB

16   deposition follows ventilation in healthy subjects.

17   Thus, the database related to particle deposition and lung disease suggests that total lung

18   deposition generally is increased with obstructed airways, regardless of deposition distribution

19   between the TB and A regions. Airflow distribution is very uneven in diseased lungs because of

20   the irregular pattern of obstruction, and there can be closure of small airways. In this situation, a

21   part of the lung is inaccessible, and particles can penetrate deeper into other, better ventilated

22   regions. Thus, deposition can be enhanced locally in regions of active ventilation, particularly in

23   the A region. The relationships between lung deposition and airway obstruction or ventilation

24   distribution were previously studied in vivo in animal models (Kim, 1989; Kim et al., 1989).

25

26   **6.2.3.4 Anatomical Variability**

27   As indicated above, variations in anatomical parameters between genders, and between

28   healthy people and those with obstructive lung disease, can affect deposition patterns. However,

29   previous analyses generally have overlooked the effect on deposition of normal interindividual

30   variability in airway structure in healthy individuals. This is an important consideration in

31   dosimetry modeling, which often is based on a single idealized structure. Studies that have

1　become available since the 1996 PM AQCD have attempted to assess the influence of such

2　variation in respiratory tract structure on deposition patterns.

3　　　The ET region is the first to contact inhaled particles and, therefore, deposition within this

4　region would reduce the amount of particles available for deposition in the lungs. Variations in

5　relative deposition within the ET region will, therefore, propagate through the rest of the

6　respiratory tract, creating differences in calculated doses from individual to individual.

7　A number of studies have examined the influence of variations in airway geometry on deposition

8　in the ET region.

9　　　Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles

10　ranging in size from 0.004 to 0.15 μm and at two constant inspiratory flow rates, 167 and

11　33 mL/s. Deposition was evaluated in relation to measures of nasal geometry as determined by

12　magnetic resonance imaging and acoustic rhinometry. They noted that interindividual variability

13　in deposition was correlated with the wide variation of nasal dimensions, in that greater surface

14　area, smaller cross-sectional area, and increasing complexity of airway shape were all associated

15　with enhanced deposition.

16　　　Using a regression analysis of data on nasal airway deposition derived from Cheng et al.

17　(1996), Guilmette et al. (1997) noted that the deposition efficiency within this region was highly

18　correlated with both nasal airway surface area and volume; this indicated that airway size and

19　shape factors were important in explaining intraindividual variability noted in experimental

20　studies of human nasal airway aerosol deposition. Thus, much of the variability in measured

21　deposition among people resulted from differences in the size and shape of specific airway

22　regions.

23　　　Kesavanathan and Swift (1998) also evaluated the influence of geometry in affecting

24　deposition in the nasal passages of normal adults from two ethnic groups. Mathematical

25　modeling of the results indicated that the shape of the nostril affected particle deposition in the

26　nasal passages, but that there still remained large intersubject variations in deposition when this

27　was accounted for, and which was likely caused by geometric variability in the mid and posterior

28　regions of the nasal passages.

29　　　Bennett et al. (1998) studied the role of anatomic dead space (ADS) in particle deposition

30　and retention in bronchial airways, using an aerosol bolus technique. They found that the

31　fractional deposition was dependant on the subject's ADS and that a significant number of

1   particles was retained beyond 24 h. This finding of prolonged retention of insoluble particles in

2   the airways is consistent with the findings of Scheuch et al. (1995) and Stahlhofen et al. (1986a)

3   and with the predictions of asymmetric stochastic human lung models (Asgharian et al., 2001).

4   Bennett et al. (1999) also found a lung volume-dependent asymmetric distribution of particles

5   between the left and right lung; the left:right ratio was increased at increased percentage of total

6   lung capacity (e.g., at 70% TLC, L:R was 1.60).

7   From the analysis of detailed deposition patterns measured by a serial bolus mouth delivery

8   method, Kim and Hu (1998) and Kim and Jaques (2000) found a marked enhancement in

9   deposition in the very shallow region (lung penetration depth <150 mL) of the lungs in females.

10   The enhanced local deposition for both ultrafine and coarse particles was attributed to a smaller

11   size of the upper airways, particularly of the laryngeal structure.

12   Hofmann et al. (2000) examined the role of heterogeneity of airway structure in the rat

13   acinar region in affecting deposition patterns within this area of the lungs. By the use of different

14   morphometric models, they showed that substantial variability in predicted particle deposition

15   would result.

16

6.2.4 Interspecies Patterns of Deposition

18   The primary purpose of this document is to assess the health effects of particles in humans.

19   As such, human dosimetry studies have been stressed. Such studies avoid uncertainties

20   associated with extrapolation of dosimetry from laboratory animals to humans. Nevertheless,

21   animal models have been and are currently being used in evaluations of health effects from

22   particulate matter because there are ethical limits to the types of studies that can be performed on

23   human subjects. Because of this, there is considerable need to understand dosimetry in animals

24   and to understand dosimetric differences between animals and humans. In this regard, there are a

25   number of newly published studies that were designed to assess particle dosimetry in commonly

26   used animals and to relate this to dosimetry in humans.

27   The various species used in inhalation toxicology studies that serve as the basis for

28   dose-response assessment may not receive identical doses in a comparable respiratory tract

29   region (i.e., ET, TB, or A) when exposed to the same aerosol at the same inhaled concentration.

30   Such interspecies differences are important because any toxic effect is often related to the

31   quantitative pattern of deposition within the respiratory tract as well as to the exposure

1   concentration; this pattern determines not only the initial respiratory tract tissue dose, but also the

2   specific pathways by which deposited material is cleared and redistributed (Schlesinger, 1985).

3   Differences in patterns of deposition between humans and animals were summarized previously

4   in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) and by others

5   (Schlesinger et al., 1997). Such differences in initial deposition must be considered when

6   relating biological responses obtained in laboratory animal studies to effects in humans.

7   It is difficult to compare systematically interspecies deposition patterns obtained from

8   various reported studies because of variations in experimental protocols, measurement

9   techniques, definitions of specific respiratory tract regions, and so on. For example, tests with

10   humans are generally conducted under protocols that standardize the breathing pattern; whereas

11   those using laboratory animals involve a wider variation in respiratory exposure conditions (e.g.,

12   spontaneous breathing versus ventilated breathing or varying degrees of sedation). Much of the

13   variability in the reported data for individual species may be due to the lack of normalization for

14   specific respiratory parameters during exposure. In addition, the various studies have used

15   different exposure techniques, such as nasal mask, oral mask, oral tube, or tracheal intubation.

16   Regional deposition is affected by the exposure route and delivery technique employed.

17   Figure 6-9 shows the regional deposition data versus particle diameter in commonly used

18   laboratory animals obtained by various investigators, as compiled by Schlesinger (1988; 1989).

19   The results are described in detail in the 1996 PM AQCD (U.S. Environmental Protection

20   Agency, 1996). In general, there is much variability in the data; however, it is possible to make

21   some generalizations concerning comparative deposition patterns. The relationship between total

22   respiratory tract deposition and particle size is approximately the same in humans and most of

23   these animals; deposition increases on both sides of a minimum that occurs for particles of 0.2 to

24   1 μm. Interspecies differences in regional deposition occur due to anatomical and physiological

25   factors. In most laboratory animal species, deposition in the ET region is near 100 percent for a

26   particle diameter (d_p) greater than 5 μm (Raabe et al., 1988), indicating greater efficiency than

27   that seen in humans. In the TB region, there is a relatively constant, but lower, deposition

28   fraction for d_p greater than 1 μm in all species compared to humans. Finally, in the A region,

29   deposition fraction peaks at a lower particle size (d_p about 1 μm) in laboratory animals than in

30   humans.

31
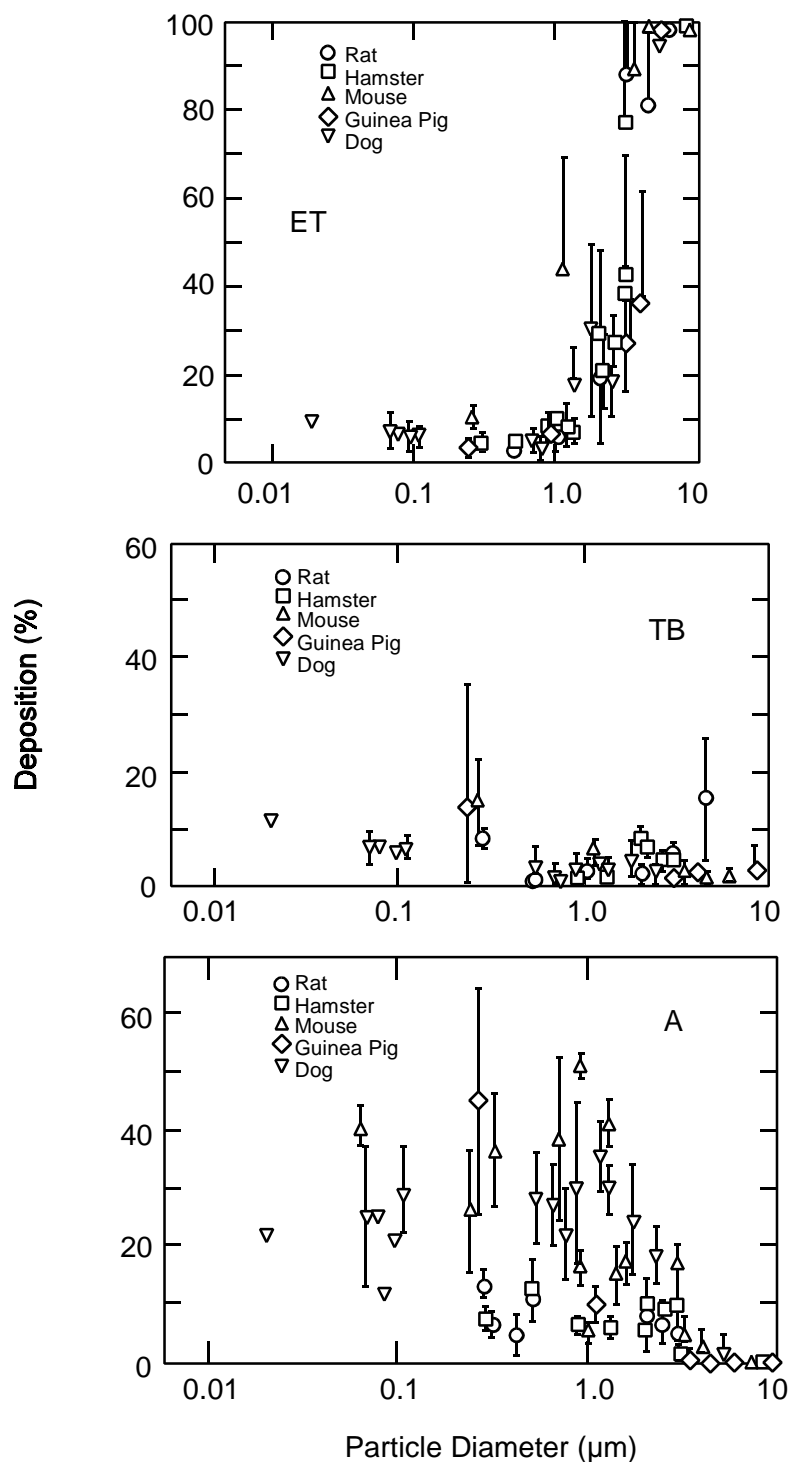
Figure 6-9. Regional deposition fraction in laboratory animals as a function of particle size. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 *μ*m and geometric (or diffusion equivalent) for those < 0.5 *μ*m.

Source: Schlesinger (1988).

1   One of the issues that must be considered in interspecies comparisons of hazards from

2   inhaled particles is inhalability of the aerosol in the atmosphere of concern. Although this may

3   not be an issue for humans per se as far as exposure to ambient particles is concerned, it can be

4   an important issue when attempting to extrapolate to humans the results of studies using animal

5   species commonly employed in inhalation toxicological studies (Miller et al., 1995).

6   For example, differences between rat and human become very pronounced for particles >5 μm,

7   and some differences are also evident for particles as small as l μm (Figure 6-10).

8   A number of studies have addressed various aspects of interspecies differences in

9   respiratory tract deposition using mathematical modeling approaches. Hofmann et al. (1996)

10   compared deposition between rat and human lungs, using three-dimensional asymmetric

11   bifurcation models and mathematical procedures for obtaining air flow and particle trajectories.

12   Deposition in segmental bronchi and terminal bronchioles was evaluated under both inspiration

13   and expiration at particle sizes of 0.01, 1.0, and 10 μm, which covers the range of deposition

14   mechanisms from diffusion to impaction. Total deposition efficiencies of all particles in the

15   upper and lower airway bifurcations were comparable in magnitude for both rat and human.

16   However, the investigators noted that penetration probabilities from preceding airways must be

17   considered. When considering the higher penetration probability in the human lung, the resulting

18   bronchial deposition fractions were generally higher in human than in rat. For all particle sizes,

19   deposition at rat bronchial bifurcations was less enhanced on the carinas compared to that found

20   in human airways.

21   Hofmann et al. (1996) attempted to account for interspecies differences in branching

22   patterns in deposition analyses. Numerical simulations of three-dimensional particle deposition

23   patterns within selected (species-specific) bronchial bifurcations indicated that morphologic

24   asymmetry was a major determinant of the heterogeneity of local deposition patterns. They noted

25   that many interspecies deposition calculations used morphometry that was described by

26   deterministic lung models (i.e., the number of airways in each airway generation is constant, and

27   all airways in a given generation have identical lengths and diameters). Such models cannot

28   account for variability and branching asymmetry of airways in the lungs. Thus, their study

29   employed computations that used stochastic morphometric models of human and rat lungs

30   (Koblinger and Hofmann, 1985, 1988; Hofmann et al., 1989b) and evaluated regional and local

31   particle deposition. Stochastic models of lung structure describe, in mathematical terms, the
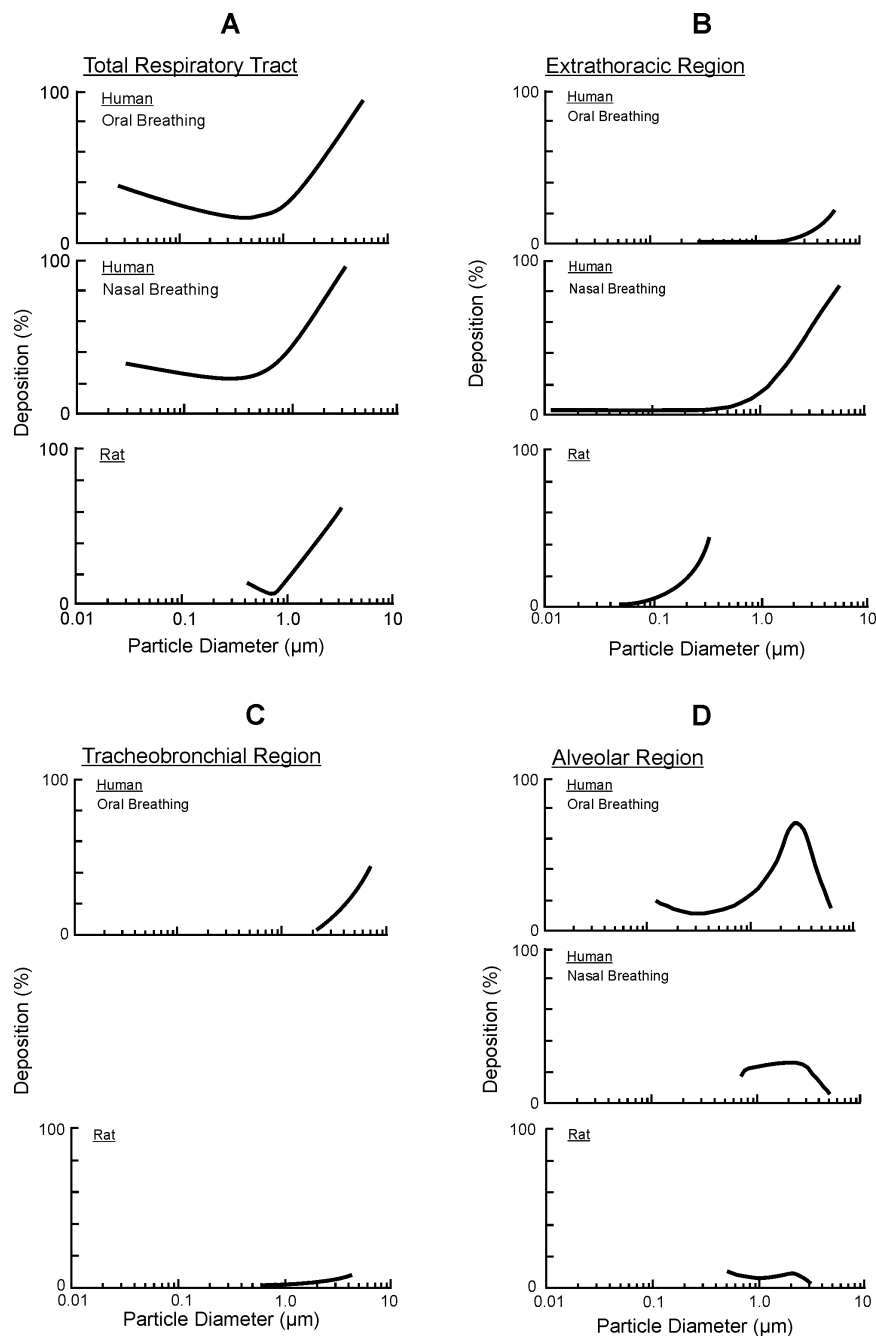
Figure 6-10. Particle deposition efficiency in rats and humans as a function of particle size for the (A) total respiratory tract, (B) thoracic region, (C) tracheobronchial region, and (D) alveolar region. Each curve represents an eye fit through mean values (or centers of ranges) for the data compiled by Schlesinger (1985). Particle diameters are aerodynamic (MMAD) for those ≥0.5 μm and geometric (or diffusion equivalent) for those < 0.5 μm.

Source: Modified from Schlesinger (1989).

inherent asymmetry and variability of the airway system, including diameter, length, and angle. They are based on statistical analyses of actual morphometric analyses of lungs. The model also incorporated breathing patterns for humans and rats. In a later analysis (Hoffmann and Bergmann, 1998), the dependence of deposition on particle size was found to be qualitatively similar in both rats and humans, with deposition minima in the size range of 0.1 to 1 μm for total deposition as well as deposition within the TB and A regions. In addition, a deposition maximum occurred at about 0.02 to 0.03 μm and between 3 and 5 μm in both species. The deposition decrease in the A region at the smallest and largest sizes resulted from the filtering efficiency of upstream airways. Although deposition patterns were qualitatively similar in rat and human, deposition in the human lung appeared to be consistently higher than in the rat in all regions of the lung (TB and A) over the entire size range. Both species showed a similar pattern of dependence of deposition on flow rate.

The above model also assessed local deposition. In both human and rat, deposition of 0.001-μm particles was highest in the upper bronchial airways; whereas 0.1- and 1-μm particles showed higher deposition in more peripheral airways, namely the bronchiolar airways in rat and the respiratory bronchioles in humans. Deposition was variable within any branching generation because of differences in airway dimensions, and regional and total deposition also exhibited intrasubject variations. Airway geometric differences between rats and humans were reflected in deposition. Because of the greater branching asymmetry in rats, prior to about generation 12, each generation showed deposition maxima at two particle sizes, reflecting deposition in major and minor daughters. These geometric differences became reduced with depth into the lung; beyond generation 12, these two maxima were no longer seen.

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

1   indicating fairly uniform deposition throughout the lungs. On the other hand, in the resting rat,

2   the ratio was 2.24, indicating greater deposition in the TB region than in the A region. However,

3   by mimicking light activity in the rat, the ratio was reduced to 0.97, similar to the human. These

4   data suggest that ventilatory characteristics in animal models may have to be adjusted to provide

5   for comparable regional deposition to that in humans.

6   The relative distribution of particles deposited within the bronchial and alveolar regions of

7   the airways may differ in the lungs of animals and humans for the same total amount of deposited

8   matter because of structural differences. The effect of such structural differences between rat and

9   human airways on particle deposition patterns was examined by Hofmann et al. (1999; 2000) in

10   an attempt to find the most appropriate morphometric parameter to characterize local particle

11   deposition for extrapolation modeling purposes. Particle deposition patterns were evaluated as

12   functions of three morphometric parameters, namely (1) airway generation, (2) airway diameter,

13   and (3) cumulative path length. It was noted that airway diameter was a more appropriate

14   morphometric parameter for comparison of particle deposition patterns in human and rat lungs

15   than was airway generation.

16   The manner in which particle dose is expressed, that is, the specific dose metric, may affect

17   relative differences in deposition between humans and other animal species. For example,

18   although deposition when expressed on a mass per unit alveolar surface area basis may not be

19   different between rats and humans, dose metrics based on particle number per various anatomical

20   parameters (e.g., per alveolus or alveolar macrophage) can differ between rats and humans,

21   especially for particles around 0.1 to 0.3 μm (Miller et al., 1995). Furthermore, in humans with

22   lung disease (such as asthma or COPD), differences between rat and human can be even more

23   pronounced.

24   The probability of any biological effect occurring in humans or animals depends on

25   deposition and retention of particles, as well as the underlying tissue sensitivity. Interspecies

26   dosimetric extrapolation must consider these differences in evaluating dose-response

27   relationships. Thus, even similar deposition patterns may not result in similar effects in different

28   species, because dose also is affected by clearance mechanisms. In addition, the total number of

29   particles deposited in the lung may not be the most relevant dose metric for interspecies

30   comparisons. For example, it may be the number of deposited particles per unit surface area or

31   dose to a specific cell (e.g., alveolar macrophage) that determines response for specific regions.

1 More specifically, even if deposition is similar in rat and human, there would be a higher

2 deposition density in the rat because of the smaller surface area of rat lung. Thus, species-

3 specific differences in deposition density should be considered when health effects observed in

4 laboratory animals are being evaluated for potential effects occurring in humans.

5

6

6.3 PARTICLE CLEARANCE AND TRANSLOCATION

8   This section discusses the clearance and translocation of particles that have deposited in the

9 respiratory tract. First, a basic overview of biological mechanisms and pathways of clearance in

10 the various region of the respiratory tract is presented. This is then followed by an update on

11 regional kinetics of particle clearance. Interspecies patterns of clearance are then addressed,

12 followed by new information on biological factors that may modulate clearance.

13

6.3.1 Mechanisms and Pathways of Clearance

15   Particles that deposit on airway surfaces may be cleared from the respiratory tract

16 completely or may be translocated to other sites within this system by various regionally distinct

17 processes. These clearance mechanisms, which are outlined in Table 6-1, can be categorized as

18 either absorptive (i.e., dissolution) or nonabsorptive (i.e., transport of intact particles) and may

19 occur simultaneously or with temporal variations. It should be mentioned that particle solubility

20 in terms of clearance refers to solubility within the respiratory tract fluids and cells. Thus, a

21 poorly soluble particle is considered to be one whose rate of clearance by dissolution is

22 insignificant compared to its rate of clearance as an intact particle. All deposited particles,

23 therefore, are subject to clearance by the same basic mechanisms, with their ultimate fate a

24 function of deposition site, physicochemical properties (including solubility and any toxicity),

25 and sometimes deposited mass or number concentration. Clearance routes from the various

26 regions of the respiratory tract have been discussed previously in detail (U.S. Environmental

27 Protection Agency, 1996; Schlesinger et al., 1997). They are schematically shown in Figure 6-11

28 (for extrathoracic and tracheobronchial regions) and in Figure 6-12 (for poorly soluble particle

29 clearance from the alveolar region) and are reviewed only briefly below.

30

TABLE 6-1. OVERVIEW OF RESPIRATORY TRACT PARTICLE CLEARANCE AND TRANSLOCATION MECHANISMS

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

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

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

Source: Schlesinger (1995).
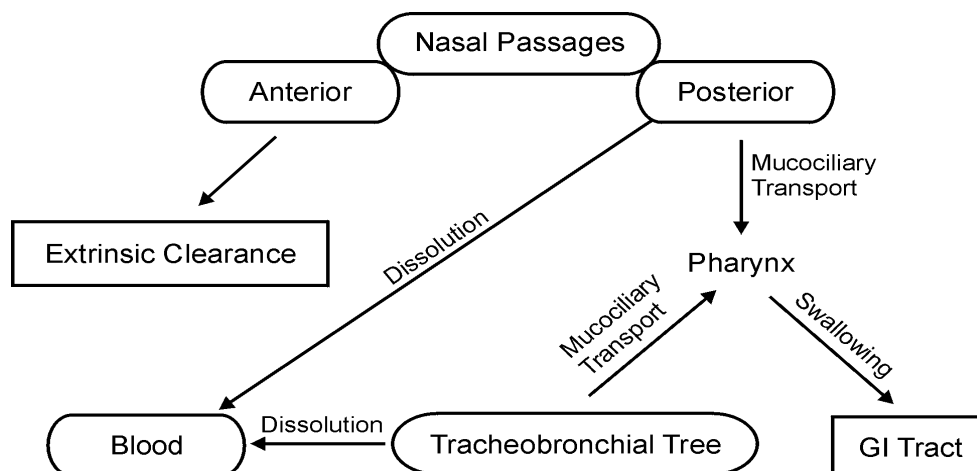
Figure 6-11.   Major clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree.

Source: Adapted from Schlesinger et al. (1997).
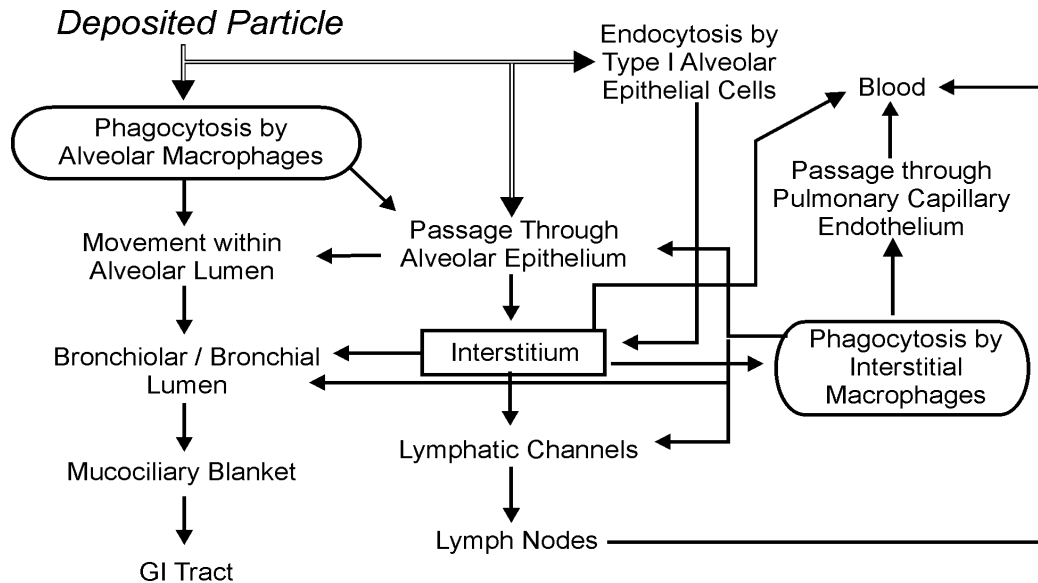
Figure 6-12. **Diagram of known and suspected clearance pathways for poorly soluble particles depositing in the alveolar region. (The magnitude of various pathways may depend upon size of deposited particle.)**

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

6.3.1.1 Extrathoracic Region

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

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

1   **6.3.1.2 Tracheobronchial Region**

2   Poorly soluble particles deposited within the TB region are cleared by mucociliary transport

3   towards the oropharynx, followed by swallowing. Poorly soluble particles also may traverse the

4   epithelium by endocytotic processes, entering the peribronchial region, be engulfed via

5   phagocytosis by airway macrophages (which can then move cephalad on the mucociliary

6   blanket), or enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles

7   may be absorbed through the epithelium into the blood. It has been shown that blood flow

8   affects translocation from the TB region, in that decreased bronchial blood flow is associated

9   with increased airway retention of soluble particles (Wagner and Foster, 2001). There is,

10   however, evidence that even soluble particles may be cleared by mucociliary transport (Bennett

11   and Ilowite, 1989; Matsui et al., 1998; Wagner and Foster, 2001).

12

13   **6.3.1.3 Alveolar Region**

14   Clearance from the A region occurs via a number of mechanisms and pathways. Particle

15   removal by macrophages comprises the main nonabsorptive clearance process in this region.

16   These cells, which reside on the epithelium, phagocytize and transport deposited material that

17   they contact by random motion or via directed migration under the influence of chemotactic

18   factors.

19   Although alveolar macrophages normally comprise up to about 5% of the total alveolar

20   cells in healthy, nonsmoking humans and other mammals, the actual cell count may be altered by

21   particle loading. The magnitude of any increase in cell number is related to the number of

22   deposited particles rather than to total deposition by weight. Thus, equivalent masses of an

23   identically deposited substance would not produce the same response if particle sizes differed,

24   and the deposition of smaller particles would tend to result in a greater elevation in macrophage

25   number than would deposition of larger particles.

26   Particle-laden macrophages may be cleared from the A region along a number of pathways.

27   As noted in Figure 6-11, this includes cephalad transport via the mucociliary system after the

28   cells reach the distal terminus of the mucus blanket; movement within the interstitium to a

29   lymphatic channel; or perhaps traversing of the alveolar-capillary endothelium, directly entering

30   the bloodstream. Particles within the lymphatic system may be translocated to tracheobronchial

31   lymph nodes, which can become reservoirs of retained material. Particles subsequently reaching

1   the postnodal lymphatic circulation will enter the blood. Once in the systemic circulation, these

2   particles, or transmigrated macrophages, can travel to extrapulmonary organs. Deposited

3   particles that are not ingested by alveolar macrophages may enter the interstitium, where they are

4   subject to phagocytosis by resident interstitial macrophages, and may travel to perivenous,

5   peribronchiolar or subpleural sites, where they become trapped, increasing particle burden. The

6   migration and grouping of particles and macrophages within the lungs can lead to the

7   redistribution of initially diffuse deposits into focal aggregates. Some particles or components

8   can bind to epithelial cell membranes or macromolecules, or to other cell components, delaying

9   clearance from the lungs.

10   Churg and Brauer (1997) examined lung autopsy tissue from 10 never-smokers from

11   Vancouver, Canada. They noted that the geometric mean particle diameter (GMPD) in lung

12   parenchymal tissue was 0.38 μm (σg = 2.4). Ultrafine particles accounted for less than 5% of the

13   total retained particulate matter. Metal particles had a GMPD of 0.17 μm, and silicates 0.49 μm.

14   Ninety-six percent of retained PM was less than 2.5 μm. A subsequent study considered

15   retention of actual ambient particles in the lungs, which is related to deposition. Brauer et al.

16   (2001) showed that small particles could undergo significant steady-state retention within the

17   lungs. Using lungs obtained at autopsy from long-term, nonsmoking residents of an area having

18   high levels of ambient PM (Mexico City, Mexico) and those from an area with relatively low PM

19   levels (Vancouver, Canada), the investigators measured the particle concentration per gram of

20   lung within the parenchyma. They found that living in the high PM region resulted in

21   significantly greater retention of both fine and ultrafine particles within the lungs; levels in the

22   lungs from Mexico City contained over 7.4 times the concentration of these particles as did the

23   lungs from residents of Vancouver. These results indicate a clear relationship between ambient

24   exposure concentration and retention in the A region.

25   Clearance by the absorptive mechanism involves dissolution in the alveolar surface fluid,

26   followed by transport through the epithelium and into the interstitium, and then diffusion into the

27   lymph or blood. Solubility is influenced by the particle's surface to volume ratio and other

28   properties, such as hydrophilicity and lipophilicity (Mercer, 1967; Morrow, 1973; Patton, 1996).

29

30

31

6.3.2 Clearance Kinetics

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

6.3.2.1 Extrathoracic Region

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

6.3.2.2 Tracheobronchial Region

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

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

1   particles retained longer than 24 h. Based upon asymmetric stochastic human lung modeling

2   data, intersubject variability in retained mass arising from the periphery of the TB can explain the

3   experimental observations while still fitting a single compartment clearance model. Other

4   studies described below, however, do support the concept that TB regional clearance consists of

5   both a fast and a slow component.

6   Falk et al. (1997) studied clearance in healthy adults using monodisperse Teflon particles

7   (6.2 μm) inhaled at two flow rates. A considerable fraction (about 50%) of particles deposited in

8   small airways had not cleared within 24 h following exposure. These particles cleared with a

9   half time of 50 days. Although the deposition sites of the particles were not confirmed

10   experimentally, calculations suggested these to be in the smaller ciliated airways. Camner et al.

11   (1997) also noted that clearance from the TB region was incomplete by 24 h postexposure and

12   suggested that this may be caused by incomplete clearance from bronchioles. Healthy adults

13   inhaled teflon particles (6, 8, and 10 μm) under low flow rates to maximize deposition in the

14   small ciliated airways. The investigators noted a decrease in 24-h retention with increasing

15   particle size, indicating a shift toward either a smaller retained fraction, deposition more

16   proximally in the respiratory tract, or both. They calculated that a large fraction, perhaps as high

17   as 75% of particles depositing in generations 12 through 16, was still retained at 24 h

18   postexposure.

19   In a study to examine retention kinetics in the tracheobronchial tree (Falk et al., 1999),

20   nonsmoking healthy adults inhaled radioactively tagged 6.1-μm particles at both a normal flow

21   rate and a slow flow rate designed to deposit particles preferentially in small ciliated airways.

22   Lung retention was measured from 24 h to 6 mo after exposure. Following normal flow rate

23   inhalation, 14% of the particles retained at 24 h cleared with a half time of 3.7 days and 86%

24   with a half time of 217 days. Following slow flow rate inhalation, 35% of the particles retained

25   at 24 h cleared with a half time of 3.6 days and 65% with a half time of 170 days. Estimates

26   using a number of mathematical models indicated higher deposition in the bronchiolar region

27   (generations 9 through 15) with the slow rate inhalation compared to the normal rate. The

28   experimental data and predictions of the deposition modeling indicated that 40% of the particles

29   deposited in the conducting airways during the slow inhalation were retained after 24 h. The

30   particles that cleared with the shorter half time were mainly deposited in the bronchiolar region,

1   but only about 25% of the particles deposited in this region cleared in this phase. This study

2   provided additional confirmation for a phase of slow clearance from the bronchial tree.

3   The underlying sites and mechanisms of long-term TB retention in the smaller airways are

4   not known. Some proposals were presented in the earlier 1996 PM AQCD (U.S. Environmental

5   Protection Agency, 1996). This slow clearing tracheobronchial compartment likely is associated

6   with bronchioles <1 mm in diameter (Lay et al., 1995; Kreyling et al., 1999; Falk et al., 1999).

7   Based on a study in which an adrenergic agonist was used to stimulate mucus flow, so as to

8   examine the role of mucociliary transport in the bronchioles, it was found that clearance from the

9   smaller airways was not influenced by the drug, suggesting to the investigators that mucociliary

10   transport was not as an effective clearance mechanism from this region as it is in larger airways

11   (Svartengren et al., 1998, 1999). Although slower or less effective mucus transport may result in

12   longer retention times in small airways, other factors may account for long-term TB retention.

13   One such proposal is the movement of particles into the gel phase because of surface tension

14   forces in the liquid lining of the small airways (Gehr et al., 1990, 1991). The issue of particle

15   retention in the tracheobronchial tree certainly is not resolved.

16   Long-term TB retention patterns are not uniform. There is an enhancement at bifurcation

17   regions (Radford and Martell, 1977; Henshaw and Fews, 1984; Cohen et al., 1988), the likely

18   result of both greater deposition and less effective mucus clearance within these areas. Thus,

19   doses calculated based on uniform surface retention density may be misleading, especially if the

20   material is toxicologically slow acting.

21

22   **6.3.2.3 Alveolar Region**

23   Particles deposited in the A region generally are retained longer than are those deposited in

24   airways cleared by mucociliary transport. There are limited data on alveolar clearance rates in

25   humans. Within any species, reported clearance rates vary widely because, in part, of different

26   properties of the particles used in the various studies. Furthermore, some chronic experimental

27   studies have employed high concentrations of poorly soluble particles that may have interfered

28   with normal clearance mechanisms, resulting in clearance rates different from those that would

29   typically occur at lower exposure levels. Prolonged exposure to high particle concentrations is

30   associated with what is termed particle "overload." This is discussed in greater detail in

31   Section 6.4.

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

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

15   Uningested particles may penetrate into the interstitium within a few hours following
16   deposition. This transepithelial passage seems to increase as particle loading increases,
17   especially to that level above which macrophage numbers increase (Ferin, 1977; Ferin et al.,
18   1992; Adamson and Bowden, 1981). It also may be particle size dependent, because insoluble
19   ultrafine particles (<0.1 μm diameter) of low intrinsic toxicity show increased access to the
20   interstitum and greater lymphatic uptake than do larger particles of the same material
21   (Oberdörster et al., 1992; Ferin et al., 1992). However, ultrafine particles of different materials
22   may not enter the interstitium to the same extent. Similarly, a depression of phagocytic activity,
23   a reduction in macrophage ability to migrate to sites of deposition (Madl et al., 1998), or the
24   deposition of large numbers of ultrafine particles may increase the number of free particles in the
25   alveoli, perhaps enhancing removal by other routes. In any case, free particles may reach the
26   lymph nodes perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al.,
27   1985) although this route is not definitive and may be species dependent.

28   The extent of lymphatic uptake of particles may depend on the effectiveness of other
29   clearance pathways, in that lymphatic translocation likely increases when phagocytic activity of
30   alveolar macrophages decreases. This may be a factor in lung overload. However, it seems that
31   the deposited mass or number of particles must exceed some threshold below which increases in

1   loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle

2   and Brieger, 1961). In addition, the rate of translocation to the lymphatic system may be

3   somewhat particle size dependent. Although no human data are available, translocation of latex

4   particles to the lymph nodes of rats was greater for 0.5- to 2-μm particles than for 5- and 9-μm

5   particles (Takahashi et al., 1992), and particles within the 3- to 15-μm size range were found to

6   be translocated at faster rates than were larger sizes (Snipes and Clem, 1981). On the other hand,

7   translocation to the lymph nodes was similar for both 0.4-μm barium sulfate or 0.02-μm gold

8   colloid particles (Takahashi et al., 1987). It seems that particles ≤ 2 μm clear to the lymphatic

9   system at a rate independent of size; and it is particles of this size, rather than those ≥ 5 μm, that

10   would have significant deposition within the A region following inhalation. In any case, the

11   normal rate of translocation to the lymphatic system is quite slow; and elimination from the

12   lymph nodes is even slower, with half times estimated in tens of years (Roy, 1989).

13   Soluble particles depositing in the A region may be cleared rapidly via absorption through

14   the epithelial surface into the blood. Actual rates depend on the size of the particle (i.e., solute

15   size), with smaller molecular weight solutes clearing faster than larger ones. Absorption may be

16   considered as a two stage process, with the first stage being dissociation of the deposited

17   particles into material that can be absorbed into the circulation (i.e., dissolution) and the second

18   stage being uptake of this material. Each of these stages may be time dependent. The rate of

19   dissolution depends on a number of factors, including particle surface area and chemical

20   structure. A portion of the dissolved material may be absorbed more slowly because of binding

21   to respiratory tract components. Accordingly, there is a very wide range for absorption rates,

22   depending on the physicochemical properties of the material deposited.

23   As indicated in both the toxicology and epidemiology chapters of this document (Chapters

24   7 and 8), one of the health outcome of concern relates to ambient PM effects on the

25   cardiovascular system. Thus, an important dosimetric issue involves the pathways by which

26   inhaled and deposited particles in the lungs could impact upon extrapulmonary systems.

27   Clearance and translocation pathways by which this may occur have been recently described.

28   Nemmar et al. (2001) instilled hamsters with radioactively-labeled colloidal albumin particles

29   (diameter ≤ 0.080 μm) as a model for ambient ultrafine particles and measured the label

30   appearing in systemic blood and various extrapulmonary organs up to 1 h postexposure. They

31   found label in blood within 5 minutes after instillation. In their subsequent studies in which

1   healthy volunteers were challenged with inhalation of ^{99m}Technitum-labeled ultrafine carbon

2   particles (Nemmar et al., 2002), the radioactivity was detected in blood as early as 1 min,

3   reaching a maximum between 10 and 20 min after inhalation of the aerosol. While label was

4   also noted in the other extrapulmonary organs examined (namely liver, heart, spleen, kidneys,

5   and brain), the liver had the highest levels and these increased with increasing time postexposure,

6   while the second highest levels were noted in the heart or kidney, depending upon the instilled

7   concentration. This suggests that ultrafine particles can rapidly diffuse from the lungs into the

8   systemic circulation, thus providing a pathway by which ambient PM may rapidly affect

9   extrapulmonary organs.

10   In another study, Takenaka et al. (2001) exposed rats by inhalation to 0.015 μm particles of

11   elemental silver and found evaluated levels of these particles in various extrapulmonary organs

12   up to 7 days postexposure. They found that the amount of particles in the lungs decreased

13   rapidly with time and, by day 7, only about 4% of the initial lung burden remained. At day 0,

14   particles were already found in the blood. The particles were found to be distributed in the liver,

15   kidney, heart, and brain by 1 day postexposure. The particle concentration was highest in the

16   kidney, followed by the liver, and then the heart. This study also indicates that inhaled ultrafine

17   particles were rapidly cleared from the lungs into the systemic circulation. However, a similar

18   cleance pattern was found after intratracheal instillation of AgNO$_3$ solution. Therefore, the

19   investigators postulated that the rapid clearance of elemental silver particles was due to a fast

20   dissolution of ultrafine silver particles into the lung fluid and subsequent diffusion into the blood

21   stream, although a possibility of direct translocation of solid particles into the blood stream was

22   not excluded. The investigators also instilled an aqueous suspension of elemental silver into

23   some animals; in this case, there was more retention in the lungs, which was ascribed to

24   phagocytic accumulation of agglomerated particles in alveolar macrophages and slow dissolution

25   of particles in cells. Thus, this study also suggested that particle size and the tendency of

26   particles to aggregate can affect the translocation pathway from the lungs. Earlier studies

27   (Huchon et al., 1987; Peterson et al., 1989; Morrison et al., 1998) investigated lung clearance of

28   labeled macromolecule solutes with widely varying molecular weight and labeled albumin, as

29   well as albumin ultrafine aggregates. Clearance rates found from these earlier studies were much

30   slower than recent studies described above, suggesting that the possibility of a fast clearing

31   pathway of solid ultrafine particles may need further study.

6.3.3 Interspecies Patterns of Clearance

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

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

Hsieh and Yu (1998) summarized the existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and human. Clearance at different initial lung burdens, ranging from 0.001 to 10 mg particles/g lung, was analyzed using a two-phase exponential decay function. Two clearance phases in the alveolar region, namely fast and slow, were associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with the lymph nodes. Rats and mice were noted to be fast clearers in comparison to the other species. Increasing the initial lung burden resulted in an increasing mass fraction of particles cleared by the slower phase. As lung burden increased

1   beyond 1 mg particles/g lung, the fraction cleared by the slow phase increased to almost 100%

2   for all species. However, the rate for the fast phase was similar in all species and did not change

3   with increasing lung burden of particles; whereas the rate for the slow phase decreased with

4   increasing lung burden. At elevated burdens, the effect on clearance rate was greater in rats than

5   in humans, an observation consistent with previous findings (Snipes, 1989).

6

7   ## 6.3.4 Factors Modulating Clearance

8   A number of factors have previously been assessed in terms of modulation of normal

9   clearance patterns, including: age, gender, workload, disease, and irritant inhalation. Such

10   factors have been discussed in detail previously (U.S. Environmental Protection Agency, 1996).

11

12   **6.3.4.1 Age**

13   Studies previously described in the 1996 PM AQCD (U.S. Environmental Protection

14   Agency, 1996) indicated that there appeared to be no clear evidence for any age-related

15   differences in clearance from the lung or total respiratory tract, either from child to adult, or

16   young adult to elderly. Studies of mucociliary function have shown either no changes or some

17   slowing in mucous clearance function with age after maturity, but at a rate that would be unlikely

18   to significantly affect overall clearance kinetics.

19

20   **6.3.4.2 Gender**

21   Previously reviewed studies (U.S. Environmental Protection Agency, 1996) indicated no

22   gender-related differences in nasal mucociliary clearance rates in children (Passali and Bianchini

23   Ciampoli, 1985) nor in tracheal transport rates in adults (Yeates et al., 1975).

24

25   **6.3.4.3 Physical Activity**

26   The effect of increased physical activity on mucociliary clearance is unresolved, with

27   previously discussed studies (U.S. Environmental Protection Agency, 1996) indicating either no

28   effect or an increased clearance rate with exercise. There are no data concerning changes in

29   A region clearance with increased activity levels. Breathing with an increased tidal volume was

30   noted to increase the rate of particle clearance from the A region, and this was suggested to result

31   from distension-related evacuation of surfactant into proximal airways, resulting in a facilitated

1   movement of particle-laden macrophages or uningested particles because of the accelerated

2   motion of the alveolar fluid film (John et al., 1994).

3

4   **6.3.4.4 Respiratory Tract Disease**

5   Various respiratory tract diseases are associated with clearance alterations. Evaluation of

6   clearance in individuals with lung disease requires careful interpretation of results, because

7   differences in deposition of particles used to assess clearance function may occur between

8   normal individuals and those with disease; this would impact directly on the measured clearance

9   rates, especially in the tracheobronchial tree. Earlier studies reported in the 1996 PM AQCD

10   (U.S. Environmental Protection Agency, 1996) noted findings of (a) slower nasal mucociliary

11   clearance in humans with chronic sinusitis, bronchiectasis, rhinitis, or cystic fibrosis and (b)

12   slowed bronchial mucus transport associated with bronchial carcinoma, chronic bronchitis,

13   asthma, and various acute respiratory infections. However, a recent study by Svartengren et al.

14   (1996a) concluded, based on deposition and clearance patterns, that particles cleared equally

15   effectively from the small ciliated airways of healthy humans and those with mild to moderate

16   asthma; but, this similarity was ascribed to effective therapy for the asthmatics.

17   In another study, Svartengren et al. (1996b) examined clearance from the TB region in

18   adults with chronic bronchitis who inhaled 6-μm Teflon particles. Based on calculations,

19   particle deposition was assumed to be in small ciliated airways at low flow and in larger airways

20   at higher flow. The results were compared to those obtained in healthy subjects from other

21   studies. At low flow, a larger fraction of particles was retained over 72 h in people with chronic

22   bronchitis compared to healthy subjects, indicating that clearance resulting from spontaneous

23   cough could not fully compensate for impaired mucociliary transport in small airways. For larger

24   airways, patients with chronic bronchitis cleared a larger fraction of the deposited particles over

25   72 h than did healthy subjects, but this was reportedly because of differences in deposition

26   resulting from airway obstruction.

27   An important mechanism of clearance from the tracheobronchial region, under some

28   circumstances, is cough. Although cough can be a reaction to an inhaled stimulus, in most

29   individuals with respiratory infections and disease, spontaneous coughing also serves to clear the

30   upper bronchial airways by dislodging mucus from the airway surface. Recent studies confirm

31   that this mechanism likely plays a significant role in clearance for people with mucus

hypersecretion, at least for the upper bronchial tree, and for a wide range of deposited particle sizes (0.5 to 5 μm) (Toms et al., 1997; Groth et al., 1997). There appears to be a general trend towards an association between the extent (i.e., number) of spontaneous coughs and the rate of particle clearance, with faster clearance being associated with a greater number of coughs (Groth et al., 1997). Thus, recent evidence continues to support cough as an adjunct to mucociliary movement in the removal of particles from the lungs of individuals with COPD. However, some recent evidence suggests that, like mucociliary function, cough-induced clearance may become depressed with worsening airway disease. Noone et al. (1999) found that the efficacy of clearance via cough in patients with primary ciliary dyskinesia (who rely on coughing for clearance because of immotile cilia) correlated with lung function (FEV1), in that decreased cough clearance was associated with decreased percentage of predicted FEV1.

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

One factor that may affect clearance of particles is the integrity of the epithelial surface lining of the lungs. Damage or injury to the epithelium may result from disease or from the inhalation of chemical irritants. Earlier studies performed with particle instillation had shown that alveolar epithelial damage in mice at the time of deposition resulted in increased translocation of inert carbon to pulmonary interstitial macrophages (Adamson and Hedgecock, 1995). A similar response was observed in a more recent assessment (Adamson and Prieditis, 1998), whereby silica (<0.3 μm) was instilled into a lung having alveolar epithelial damage (as evidenced by increased permeability) and particles were noted to reach the interstitium and lymph nodes.

6.4 PARTICLE OVERLOAD

Experimental studies using some laboratory rodents have employed high exposure concentrations of relatively nontoxic, poorly soluble particles. These particle loads interfered

1   with normal clearance mechanisms, producing clearance rates different from those that would

2   occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated

3   with a phenomenon that has been termed particle "overload", defined as the overwhelming of

4   macrophage-mediated clearance by the deposition of particles at a rate that exceeds the capacity

5   of that clearance pathway. It has been suggested that, in the rat, overload is more dependent

6   upon the volume rather than the mass of particles (Tran et al., 2000) and that volumetric

7   overloading will begin when particle retention approaches 1 mg particles/g lung tissue (Morrow,

8   1988). Overload is a nonspecific effect noted in experimental studies using many different kinds

9   of poorly soluble particles and results in A region clearance slowing or stasis, with an associated

10 chronic inflammation and aggregation of macrophages in the lungs and increased translocation of

11 particles into the interstitium.

12   The relevance of lung overload to humans exposed to poorly soluble, nonfibrous particles

13 remains unclear. Although it is likely to be of little relevance for most "real world" ambient

14 exposures, it may be of concern in interpreting some long-term experimental exposure data and,

15 perhaps, also for occupational exposures. For example, it has been suggested that a condition

16 called progressive massive fibrosis, which is unique to humans, has features indicating that dust

17 overload is a factor in its pathogenesis (Green, 2000). This condition is associated with

18 cumulative dust exposure and impaired clearance and can occur following high exposure

19 concentrations associated with occupational situations. In addition, any relevance to humans is

20 clouded by the suggestion that macrophage-mediated clearance is normally slower, and perhaps

21 of less relative importance in overall clearance, in humans than in rats (Morrow, 1994), and that

22 there can be significant differences in macrophage loading between species. On the other hand,

23 overload may be a factor in individuals with compromised lungs even under normal exposure

24 conditions. Thus, it has been hypothesized (Miller et al., 1995) that localized overload of particle

25 clearance mechanisms in people with compromised lung status may occur, whereby clearance is

26 overwhelmed and results in morbidity or mortality from particle exposure.

27

28

29

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

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

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

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

1   whereas intratracheal instillation produces an heterogeneous distribution, in that the periphery of

2   the lung receives little particle load and most of the instilled particles are found in regions that

3   have a short path length from the major airways. Furthermore, inhalation results in greater

4   deposition in apical areas of the lungs and less in basal areas; whereas intratracheal instillation

5   results in less apical than basal deposition. Thus, toxicological effects from instilled materials

6   may not represent those which would occur following inhalation, due to differences in sites of

7   initial deposition following exposure. In addition, instillation studies generally deliver high

8   doses to the lungs, much higher than those which would occur with realistic inhalation exposure.

9   This would also clearly affect the initial dose delivered to target tissue and its relevance to

10 ambient exposure.

11   Comparison of the kinetics of clearance of particles administered by instillation or

12 inhalation have shown similarities, as well as differences, in rates for different clearance phases,

13 depending on the exposure technique used (Oberdörster et al., 1997). However, some of the

14 differences in kinetics may be explained by differences in the initial sites of deposition. One of

15 the major pathways of clearance involves particle uptake and removal via pulmonary

16 macrophages. Dorries and Valberg (1992) noted that inhalation resulted in a lower percentage of

17 particles recovered in lavaged cells and a more even distribution of particles among

18 macrophages. More individual cells received measurable amounts of particles via inhalation than

19 via intratracheal instillation; whereas with the latter, many cells received little or no particles and

20 others received very high burdens. Furthermore, with intratracheal instillation, macrophages at

21 the lung periphery contained few, if any, particles; whereas cells in the regions of highest

22 deposition were overloaded, reflecting the heterogeneity of particle distribution when particles

23 are administered via instillation. Also, both the relative number of particles phagocytized by

24 macrophages as well as the percentage of these cells involved in phagocytosis is affected by the

25 burden of administered particles, which is clearly different in instillation and inhalation (Suarez

26 et al., 2001). Thus, when guinea pigs were administered latex microspheres (1.52-3.97 μm

27 MMAD) by inhalation or instillation, the percentage of cells involved in phagocytosis, as well as

28 the amount of particles per cell, were both significantly higher with the latter route. The route of

29 exposure, therefore, influences particle distribution in the macrophage population and could, by

30 assumption, influence clearance pathways and clearance kinetics.

1   In summary, inhalation may result in deposition within the ET region, the extent of which

2   depends on the size of the particles used. Of course, intratracheal instillation bypasses this

3   portion of the respiratory tract and delivers particles directly to the tracheobronchial tree.

4   Although some studies indicate that short (0 to 2 days) and long (100 to 300 days postexposure)

5   phases of clearance of insoluble particles delivered either by inhalation or intratracheal

6   instillation are similar, other studies indicate that the percentage retention of particles delivered

7   by instillation is greater than that for inhalation at least up to 30 days postexposure. Thus, there

8   is some inconsistency in this regard.

9   Perhaps the most consistent conclusion regarding differences between inhalation and

10   intratracheal instillation is related to the intrapulmonary distribution of particles. Inhalation

11   generally results in a fairly homogeneous distribution of particles throughout the lungs. On the

12   other hand, instillation results in a heterogeneous distribution, especially within the alveolar

13   region, and focally high concentrations of particles. The bulk of instilled material penetrates

14   beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of

15   particles. This difference is reflected in particle burdens within macrophages, with those from

16   animals inhaling particles having more homogeneous burdens and those from animals with

17   instilled particles showing groups of cells with no particles and others with heavy burdens. This

18   difference impacts on clearance pathways, dose to cells and tissues, and systemic absorption.

19   Exposure method, thus, clearly influences dose distribution.

20

21

22   **6.6 MODELING THE DISPOSITION OF PARTICLES IN THE**
23   **RESPIRATORY TRACT**

24   **6.6.1 Modeling Deposition, Clearance, and Retention**

25   Over the years, mathematical models for predicting deposition, clearance and, ultimately,

26   retention of particles in the respiratory tract have been developed. Such models help interpret

27   experimental data and can be used to make dosimetry predictions for cases where data are not

28   available. In fact, model predictions described below are estimates based on the best available

29   models at the time of publication and, except where noted, have not been verified by

30   experimental data.

1   A review of various mathematical deposition models was given by Morrow and Yu (1993)

2   and in U.S. Environmental Protection Agency (1996). There are three major elements involved

3   in mathematical modeling. First, a structural model of the airways must be specified in

4   mathematical terms. Second, deposition efficiency in each airway must be derived for each of

5   the various deposition mechanisms. Finally, a computational procedure must be developed to

6   account for the transport and deposition of the particles in the airways. As noted earlier, most

7   models are deterministic, in that particle deposition probabilities are calculated using anatomical

8   and airflow information on an airway generation by airway generation basis. Other models are

9   stochastic, whereby modeling is performed using individual particle trajectories and finite

10 element simulations of airflow.

11   Recent reports involve modeling the deposition of ultrafine particles and deposition at

12 airway bifurcations. Zhang and Martonen (1997) used a mathematical model to simulate

13 diffusion deposition of ultrafine particles in the human upper tracheobronchial tree and compared

14 the results to those in a hollow cast obtained by Cohen et al. (1990). The model results were in

15 good agreement with experimental data. Zhang and Martonen (1997) studied the inertial

16 deposition of particles in symmetric three-dimensional models of airway bifurcations,

17 mathematically examining effects of geometry and flow. They developed equations for use in

18 predicting deposition based on Stokes numbers, Reynolds numbers, and bifurcation angles for

19 specific inflows.

20   Models for deposition, clearance, and dosimetry of the respiratory tract of humans have

21 been available for the past four decades. For example, the International Commission on

22 Radiological Protection (ICRP) has recommended three different mathematical models during

23 this time period (International Commission on Radiological Protection, 1960, 1979, 1994).

24 These models make it possible to calculate the mass deposition and retention in different parts

25 the respiratory tract and provide, if needed, mathematical descriptions of the translocation of

26 portions of the deposited material to other organs and tissues beyond the respiratory tract.

27 A somewhat simplified variation of the 1994 ICRP dosimetry model was used by Snipes et al.

28 (1997) to predict average particle deposition in the ET, T and A regions and retention patterns in

29 the A region, under a repeated exposure situation for two characterized environmental aerosols

30 obtained from Philadelphia, PA and Phoenix, AZ. Both of these aerosols had both fine and

31 coarse particles. They found similar retention for the fine particles in both aerosols, but

significantly different retention for the coarse-mode particles. Because the latter type dominated
the aerosol in the Phoenix sample, this type of evaluation can be used to improve understanding
of the relationship between exposures to ambient PM and retention patterns that affect health
endpoints in residents of areas in which the particle distributions and, therefore, the particle
chemistry may differ.

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

Musante and Martonen (2000c) developed an age-dependent theoretical model to predict
dosimetry in the lungs of children. The model comprises dimensions of individual airways and
geometry of branching airway networks within developing lungs and breathing parameters as a
function of age. The model suggests that particle size, age, and activity level markedly affect
deposition patterns of inhaled particles. Simulations thus far predict a lung deposition fraction of
38% in an adult and 73% (nearly twice as high) in a 7-mo-old for 2 μm particles inhaled during
heavy breathing. The authors conclude that this model will be useful for estimating dose
delivered to sensitive subpopulations, such as children.

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

1   sedimentation. The authors conclude that particle deposition is complicated by the presence of

2   airway disease, but that the effects are systematic and predictable.

3   Segal et al. (2000b) have used a traditional mathematical model based on Weibel's lung

4   morphology and calculated total lung deposition fraction of 1 to 5 μm diameter particles in

5   healthy adults. Airway dimensions were scaled by individual lung volume. Deposition

6   predictions were made with both plug flow and parabolic flow profiles in the airways. The

7   individualized airway dimension improved the accuracy of the predicted values when compared

8   with experimental data. There were significant differences, however, between the model

9   predictions and experimental data depending on the flow profiles used, indicating that use of

10   more realistic parameters is essential to improving the accuracy of model predictions.

11   Broday and Georgopoulos (2001) presented a model that solves a variant of the general

12   dynamic equation for size evolution of respirable particles within human tracheobronchial

13   airways. The model considers polydisperse aerosols with respect to size but heterosperse with

14   respect to thermodynamic state and chemical composition. The aerosols have an initial bimodal

15   lognormal size distribution that evolves with time in response to condensation-evaporation and

16   deposition processes. Simulations reveal that submicron size particles grow rapidly and cause

17   increased number and mass fractions of the particle population to be found in the intermediate

18   size range. Because deposition by diffusion decreases with increasing size, hygroscopic fine

19   particles may persist longer in the inspired air than nonhygroscopic particles of comparable initial

20   size distribution. In contrast, the enhanced deposition probability of hygroscopic particles

21   initially from the intermediate size range increases their fraction deposited in the airways. The

22   model demonstrates that the combined effect of growth and deposition tends to decrease the

23   nonuniformity of the persistent aerosol, forming an aerosol which is characterized by size

24   distribution of smaller variance. These factors also alter the deposition profile along airways.

25   Lazaridis et al. (2001) developed a deposition model for humans that was designed to better

26   describe the dynamics of respirable particles within the airways. The model took into account

27   alterations in aerosol particle size and mass distribution that may result from processes such as

28   nucleation, condensation, coagulation, and gas phase chemical reactions. The airway geometry

29   used was the regular dichotomous model of Weibel, and it incorporated the influences of airway

30   boundary layers on particle dynamics, although simplified velocity profiles were used so as to

31   maintain a fairly uncomplicated description of respiratory physiology. Thus, this model was

1   considered to be an improvement over previous models which did not consider either the effects

2   of boundary layers on both the airborne and deposited particles or the effects of gas-phase

3   transport processes, because it can account for the polydispersity, multimodality, and

4   heterogeneous composition of common ambient aerosols. The authors indicate that the model

5   predictions were both qualitatively and quantitatively consistent with experimental data for

6   particle deposition within the TB and A regions.

7   Another respiratory tract dosimetry model was developed concurrently with the ICRP

8   model by the National Council on Radiation Protection and Measurements (NCRP, 1997).

9   As with the ICRP model (International Commission on Radiological Protection, 1994), the

10   NCRP model addresses inhalability of particles, revised subregions of the respiratory tract,

11   dissolution-absorption as an important aspect of the model, and body size and age. The NCRP

12   model defines the respiratory tract in terms of a naso-oro-pharyngo-laryngeal (NOPL) region, a

13   tracheobronchial (TB) region, a pulmonary (P) region, and lung-associated lymph nodes (LN).

14   Deposition and clearance are calculated separately for each of these regions. As with the 1994

15   ICRP model, inhalability of aerosol particles is considered, and deposition in the various regions

16   of the respiratory tract is modeled using methods that relate to mechanisms of inertial impaction,

17   sedimentation, and diffusion.

18   Fractional deposition in the NOPL region was developed from empirical relationships

19   between particle diameter and air flow rate. Deposition in the TB and P regions were projected

20   from model calculations, based on geometric or aerodynamic particle diameter and physical

21   deposition mechanisms such as impaction, sedimentation, diffusion, and interception.

22   Deposition in the TB and P regions used the lung model of Yeh and Schum (1980) with a method

23   of calculation similar to that of Findeisen (1935) and Landahl (1950). This method was modified

24   to accomodate an adjustment of lung volume and substitution of realistic deposition equations.

25   These calculations were based on air flow information and idealized morphometry and used a

26   typical pathway model. Comparison of regional deposition fraction predictions between the

27   NCRP and ICRP models was provided in U.S. Environmental Protection Agency (1996). The

28   definition of inhalability was that of the American Conference of Governmental Industrial

29   Hygenists (1985). Breathing frequency, tidal volume, and functional residual capacity were the

30   ventilatory factors used to model deposition. These were related to body weight and to three

31   levels of physical activity, namely low activity, light exertion, and heavy exertion.

1   Clearance from all regions of the respiratory tract was considered to result from
2   competitive mechanical and absorptive mechanisms. Mechanical clearance in the NOPL and TB
3   regions was considered to result from mucociliary transport. This was represented in the model
4   as a series of escalators moving towards the glottis and where each airway had an effective
5   clearance velocity. Clearance from the P region was represented by fractional daily clearance
6   rates to the TB region, the pulmonary LN region, and the blood. A fundamental assumption in
7   the model was that the rates for absorption into blood were the same in all regions of the
8   respiratory tract; the rates of dissolution-absorption of particles and their constituents were
9   derived from clearance data primarily from laboratory animals. The effect of body growth on
10   particle deposition also was considered in the model, but particle clearance rates were assumed to
11   be independent of age. Some consideration for compromised individuals was incorporated into
12   the model by altering normal rates for the NOPL and TB regions.

13   Mathematical deposition models for a number of nonhuman species have been developed;
14   these were discussed previously in the 1996 PM AQCD (U.S. Environmental Protection Agency,
15   1996). Despite difficulties, modeling studies in laboratory animals remain a useful step in
16   extrapolating exposure-dose-response relationships from laboratory animals to humans.

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

24   It is important to evaluate these accumulation patterns, especially when assessing ambient
25   chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled
26   particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined
27   as "species-dependent concentrations of airborne particles which, when chronically inhaled,
28   produce equal lung deposits of inhaled particles per gram of lung during a specified exposure
29   period" (Schlesinger et al., 1997). Available data and approaches to evaluate exposure
30   atmospheres that produce similar respiratory tract burdens in laboratory animals and humans
31   were discussed in detail in the 1996 PM AQCD.

1   Several laboratory animal models have been developed to help interpret results from

2 specific studies that involved chronic inhalation exposures to nonradioactive particles (Wolff

3 et al., 1987; Strom et al., 1988; Stöber et al., 1994). These models were adapted to data from

4 studies involving high level chronic inhalation exposures in which massive lung burdens of low

5 toxicity, poorly soluble particles were accumulated. Koch and Stöber (2001) further adapted

6 clearance models for more relevant particle deposition in the pulmonary region. They published

7 a pulmonary retention model that accounts for dissolution and macrophage-mediated removal of

8 deposited polydisperse aerosol particles. The model provides a mathematical solution for the

9 size distribution of particles in the surfactant layer of the alveolar surface and in the cell plasma

10 of alveolar macrophages and accounts for the different kinetics and biological effects in the two

11 compartments. It does not, however, account for particle penetration to the lung interstitium and

12 particle clearance by the lymph system.

13   The multiple-path models of Anjilvel and Asgharian (1995) for rat lung and its extension

14 by Subramaniam et al. (1999) for human lungs describe a method for calculating a deposited

15 fraction for a specific size distribution based on a summary of published data on regional

16 deposition of different size particles. The method is based on constructing nomograms that are

17 used to estimate alveolar deposition fractions for three species (human, monkey, and rat). The

18 data are then incorporated into a regression model that calculates more exact deposition fractions

19 in the whole lung for monodisperse and polydisperse aerosols for ultrafine through coarse

20 particle sizes. The model is somewhat constrained at present because of limitations in the

21 underlying deposition database.

22   Tran et al. (1999) used a mathematical model of clearance and retention in the A region of

23 rats lungs to determine the extent to which a sequence of clearance mechanisms and pathways

24 could explain experimental data obtained from inhalation studies using relatively insoluble

25 particles. These pathways were phagocytosis by macrophages with subsequent clearance,

26 transfer of particles into the interstitium and to lymph nodes, and overloading of defense

27 mechanisms. The model comprised a description of the complete defense system in this region,

28 using both clearance and transfer processes represented by sets of equations. The authors suggest

29 that the model could be used to examine the consistency of various hypotheses concerning the

30 fate of inhaled particles and could be used for species other than the rat with appropriate scaling.

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

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

20

21   **6.6.2 Models To Estimate Retained Dose**

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

28   An important factor in using models to predict retention patterns in laboratory animals or
29   humans is the dissolution-absorption rate of the inhaled material. Factors that affect the
30   dissolution of materials or the leaching of their constituents in physiological fluids and the
31   subsequent absorption of these constituents are not fully understood. Solubility is known to be

1   influenced by the surface-to-volume ratio and other surface properties of particles (Mercer, 1967;

2   Morrow, 1973). The rates at which dissolution and absorption processes occur are influenced by

3   factors that include the chemical composition of the material. Temperature history of materials is

4   also an important consideration for some metal oxides. For example, in controlled laboratory

5   environments, the solubility of oxides usually decreases when the oxides are produced at high

6   temperatures, which generally results in compact particles having small surface-to-volume ratios.

7   It is sometimes possible to accurately predict dissolution-absorption characteristics of materials

8   based on physical/chemical considerations, but predictions for in-vivo dissolution-absorption

9   rates for most materials, especially if they contain multivalent cations or anions, should be

10   confirmed experimentally.

11   Phagocytic cells, primarily macrophages, clearly play a role in dissolution-absorption of

12   particles retained in the respiratory tract (Kreyling, 1992). Some particles dissolve within the

13   phagosomes because of the acidic milieu in those organelles (Lundborg et al., 1984, 1985), but

14   the dissolved material may remain associated with the phagosomes or other organelles in the

15   macrophage rather than diffuse out of the macrophage to be absorbed and transported elsewhere

16   (Cuddihy, 1984). This same phenomenon has been reported for organic materials. For example,

17   covalent binding of benzo[a]pyrene or metabolites to cellular macromolecules resulted in an

18   increased alveolar retention time for that compound after inhalation exposures of rats (Medinsky

19   and Kampcik, 1985). Understanding these phenomena and recognizing species similarities and

20   differences are important for evaluating alveolar retention and clearance processes and for

21   interpreting the results of inhalation studies.

22   Dissolution-absorption of materials in the respiratory tract is clearly dependent on the

23   chemical and physical attributes of the material. Although it is possible to predict rates of

24   dissolution-absorption, it is prudent to determine this important clearance parameter

25   experimentally. It is important to understand the impact of this clearance process for the lungs,

26   tracheobronchial lymph nodes, and other body organs that might receive particles or their

27   constituents that enter the circulatory system from the lung.

28   Insufficient data were available to adequately model long-term retention of particles

29   deposited in the conducting airways of any mammalian species at the time of the 1996 PM

30   AQCD, and this still remains the case. Additional research must be done to provide the

31   information needed to properly evaluate retention of particles in conducting airways. However,

1   a number of earlier studies, discussed in the 1996 document and in Section 6.2.2.2 herein, noted

2   that some particles were retained for relatively long times in the tracheobronchial regions,

3   effectively contradicting the general conclusion that almost all inhaled particles that deposit in

4   the TB region clear within hours or days. These studies have demonstrated that variable portions

5   of the particles that deposit in, or are cleared through, the TB region are retained with half times

6   on the order of weeks or months. Long-term retention and clearance patterns for particles that

7   deposit in the ET and TB regions must continue to be thoroughly evaluated because of the

8   implications of this information for respiratory tract dosimetry and risk assessment.

9   Model projections are possible for the A region using the cumulative information in the

10   scientific literature relevant to deposition, retention, and clearance of inhaled particles.

11   Clearance parameters for six laboratory animal species were summarized in U.S. Environmental

12   Protection Agency (1996). Nikula et al. (1997) evaluated results in rats and monkeys exposed to

13   high levels of either diesel soot or coal dust. Although the total amount of retained material was

14   similar in both species, the rats retained a greater portion in the lumens of the alveolar ducts and

15   alveoli than did monkeys; whereas the monkeys retained a greater portion of the material in the

16   interstitium. The investigators concluded that intrapulmonary retention patterns in one species

17   may not be predictive of those in another species at high levels of exposure, but this may not be

18   the case at lower levels of exposure.

19   The influence of exposure concentration on the pattern of particle retention in rats (exposed

20   to diesel soot) and humans (exposed to coal dust) was examined by Nikula et al. (2000) using

21   histological lung sections obtained from both species. The exposure concentrations for diesel

22   soot were 0.35, 3.5, or 7.0 μg/m^3, and exposure duration was 7 h/day, 5 days/week for 24 mo.

23   The human lung sections were obtained from nonsmoking nonminers, nonsmoking coal miners

24   exposed to levels ≤ 2 μg dust/m^3 for 3 to 20 years, or nonsmoking miners exposed to <10 μg/m^3

25   for 33 to 50 years. In both species, the amount of retained material (using morphometric

26   techniques based on the volume density of deposition) increased with increasing dose (which is

27   related to exposure duration and concentration). In rats, the diesel exhaust particles were found

28   to be primarily in the lumens of the alveolar duct and alveoli; whereas in humans, retained dust

29   was found primarily in the interstitial tissue within the respiratory acini.

30

31

6.6.3 Fluid Dynamics Models for Deposition Calculations

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

Airflow patterns within the lung are determined by the interplay of structural and ventilatory conditions. These flow patterns govern the deposition kinetics of entrained particles in the inspired air. A number of CFD software programs are available to simulate airflow patterns in the lung by numerically solving the Navier-Stokes equations (White, 1974). The CFD modeling requires a computer reconstruction of the appropriate lung region and the application of boundary conditions. The flow field resulting from the CFD modeling is represented by velocity vectors in the grid points of a two- or three-dimensional mesh. Numerical models of particle deposition patterns are computed by simulating the trajectories of particles introduced into these

1   flow streams after solving for the particles' equation of motion. Such CFD models have been

2   developed for different regions of the respiratory tract, including the nasal cavity (Yu et al., 1998;

3   Sarangapani and Wexler, 2000); larynx (Martonen et al. 1993; Katz et al., 1997; Katz, 2001);

4   major airway bifurcations (Gradon and Orlicki, 1990; Balásházy and Hofmann, 1993a,b, 1995,

5   2001; Heistracher and Hofmann, 1995; Lee et al., 1996; Zhang et al., 1997, 2000, 2001, 2002;

6   Comer et al., 2000, 2001a,b); and alveoli (Tsuda et al., 1994a,b; Chantal, 2001).

7   Kimbell (2001) has recently reviewed the literature on CFD models of the upper respiratory

8   tract (URT). Most of these models have focused on characterizing the airflow patterns in the

9   URT and have not included simulation of particulate dosimetry. Keyhani et al. (1995) were the

10   first to use computer-aided tomography (CAT) scans of the human nasal cavity to construct an

11   anatomically accurate three-dimensional airflow model of the human nose. Subramaniam et al.

12   (1998) used MRI scan data to extend these CFD studies to include the nasopharynx. However,

13   neither of these studies investigated particle deposition in the upper respiratory tract.

14   Yu et al. (1998) have developed a three-dimensional CFD model of the entire human upper

15   respiratory tract, including the nasal airway, oral airway, laryngeal airway, and the first two

16   generations of the tracheobronchial airway. They have used this CFD model to investigate the

17   effect of breathing pattern, i.e., nasal breathing, oral breathing, and simultaneous nasal and oral

18   breathing, on airflow and ultrafine particle deposition. They concluded that the ultrafine particle

19   deposition simulated using the CFD model was in reasonable agreement with the corresponding

20   experimental measurements. In a study led by Sarangapani and Wexler (2000), an upper

21   respiratory tract CFD model that included the nasal cavity, nasopharynx, pharynx, and larynx was

22   developed to study the deposition efficiency of hygroscopic and non-hygroscopic particles in this

23   region. They used the CFD model to simulate the temperature and water vapor conditions in the

24   upper airways and predicted high relative humidity conditions in this region. They also

25   simulated particle trajectories for 0.5 μm, 1 μm, and 5 μm particles under physiologically

26   realistic flow rates. The predictions of the CFD model indicated that high relative humidity

27   conditions contribute to rapid growth of hygroscopic particles and would dramatically alter the

28   deposition characteristics of ambient hygroscopic aerosols.

29   Stapleton et al. (2000) investigated deposition of a polydisperse aerosol (MMD = 4.8 μm

30   and GSD = 1.65) in a replica of a human mouth and throat, using both experimental results and

31   3-D CFD simulation. They found that CFD results were comparable with experimental results

for a laminar flow case but were more than 200% greater for a turbulent flow case. The results
suggest that accurate predictions of particle deposition in a complex airway geometry requires a
careful evaluation of geometric and fluid dynamic factors in developing CFD models.

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

In a subsequent CFD analysis, a three-dimensional model of the larynx based on
measurements of human replica laryngeal casts (Martonen and Lowe, 1983; Katz and Martonen,
1996; Katz et al., 1997) simulated the flow field in the larynx and trachea under steady
inspiratory flow conditions at three flow rates. They observed that the complex geometry
produces jets, recirculation zones, and circumferential flow that may directly influence particle
deposition at select sites within the larynx and tracheobronchial airways. The primary
characteristics of the simulated flow field were a central jet penetrating into the trachea created
by the ventricular and vocal folds, a recirculating zone downstream of the vocal folds, and a
circumferential secondary flow. Recently, a computational model for fluid dynamics and particle
motion for inspiratory flow through the human larynx and trachea has been described (Katz,
2001). This model calculates the trajectory of single particles introduced at the entrance to the
larynx using a stochastic model for turbulent fluctuations incorporated into the particles'
equation of motion and time-averaged flow fields in the larynx and trachea. The effects of flow
rate and initial particle location on overall deposition were presented in the form of probability
density histograms of final particle deposition sites. At present, however, there are no
experimental data to validate results of such modeling.

1   A number of CFD models have been developed to study fluid flow and particle deposition

2   patterns in airway bifurcations. The bifurcation geometries that have been modeled include:

3   two-dimensional (Li and Ahmadi, 1995); idealized three-dimensional using circular airways

4   (Kinsara et al., 1993) or square channels (Asgharian and Anjilvel, 1994); symmetric bifurcations

5   (Balásházy and Hofmann, 1993a,b); or physiologically realistic asymmetric single (Balásházy

6   and Hofmann, 1995; Heistracher and Hofmann, 1995) and multiple bifurcation models (Lee

7   et al., 1995; Heistracher and Hofmann, 1997; Comer et al., 2000, 2001; Zhang et al., 2000, 2001,

8   2002), with anatomical irregularities such as cartilaginous rings (Martonen et al., 1994a) and

9   carinal ridge (Martonen et al., 1994b; Comer et al., 2001a) shapes incorporated. The CFD flow

10   simulations in the bifurcating geometry models show distinct asymmetry in the axial (primary)

11   and radial (secondary) velocity profile in the daughter and parent airway during inspiration and

12   expiration, respectively. In a systematic investigation of flow patterns in airway bifurcations,

13   numerical simulations were performed to study primary flow (Martonen et al., 2001a), secondary

14   currents (Martonen et al., 2001b), and localized flow conditions (Martonen et al., 2001c) for

15   different initial flow rates. The effects of inlet conditions, Reynolds numbers, ratio of airway

16   diameters, and branching angles with respect to intensity of primary flow, vortex patterns of the

17   secondary currents, and reverse flow in the parent-daughter transition region were investigated.

18   These simulated flow patterns match experimentally-observed flow profiles in airway

19   bifurcations (Schroter and Sudlow, 1969).

20   Gradon and Orlicki (1990) computed the local deposition flux of submicron size particles

21   in a three-dimensional bifurcation model for both inhalation and exhalation; and they found

22   enhanced deposition in the carinal ridge region during inspiration and in the central zone of the

23   parent airway during expiration. Numerical models of particle deposition in symmetric three-

24   dimensional bifurcations were developed by Balásházy and Hofmann (1993a,b), and these were

25   subsequently extended to incorporate effects of asymmetry in airway branching (Balásházy and

26   Hofmann, 1995) and physiologically realistic shapes of the bifurcation transition zone and the

27   carinal ridge (Heistracher and Hofmann, 1995; Balásházy and Hofmann, 2001). In these

28   numerical models, three-dimensional airflow patterns were computed by finite difference or

29   finite volume methods, and the trajectories of particles entrained in the airstream were simulated

30   using Monte Carlo techniques considering the simultaneous effects of gravitational settling,

31   inertial impaction, Brownian motion, and interception. The spatial deposition pattern of inhaled

1 particles was examined for a range of particle sizes (0.01-10 μm) and flow rates (16-32 L/min

2 minute volume) by determining the intersection of particle trajectories with the surrounding

3 surfaces. The overall deposition rates derived using the CFD models correspond reasonably with

4 experimental data (Kim and Iglesias, 1989). These simulations predict deposition hot spots at the

5 inner side of the daughter airway downstream of the carinal ridge during inspiration,

6 corresponding to the secondary fluid motion of the inhaled air stream. During exhalation, the

7 CFD models predict enhanced deposition at the top and bottom parts of the parent airway,

8 consistent with secondary motion in the exhaled air stream. These studies indicate that

9 secondary flow patterns within the bifurcating geometry play a dominant role in determining

10 highly non-uniform local particle deposition patterns.

11   Zhang et al. (1997) numerically simulated particle deposition in three-dimensional

12 bifurcating airways (having varying bifurcation angles) due to inertial impaction during

13 inspiration for a wide range of Reynolds numbers (100-1000). Inlet velocity profile, flow

14 Reynolds number, and bifurcation angle had a substantial effect on particle deposition efficiency.

15 Based on the simulated results, equations were derived for particle deposition efficiency as a

16 function of nondimensional parameters, such as Stokes number, Reynolds number, and

17 bifurcation angle, and were shown to compare favorably with available experimental results.

18 More recently, Comer et al. (2000) have estimated the deposition efficiency of 3, 5, and 7 μm

19 particles in a three-dimensional double bifurcating airway model for both in-plane and out-of-

20 plane configurations for a wide range of Reynolds numbers (500-2000). They demonstrated

21 deposition in the first bifurcation to be higher than in the second bifurcation, with deposition

22 mostly concentrated near the carinal region. The non-uniform flow generated by the first

23 bifurcation had a dramatic effect on the deposition pattern in the second bifurcation. Based on

24 these results, they concluded that use of single bifurcation models are inadequate to capture the

25 complex fluid-particle interactions that occur in multigeneration airway systems.

26   Comer et al. (2001a) further investigated detailed characteristics of the axial and secondary

27 flow in a double bifurcation airway model using 3-D CFD simulation. Effects of carina shape

28 (sharp vs. rounded) and bifurcation plane (planar vs. non-planar) were examined. Particle

29 trajectories and deposition patterns were subsequently investigated in the same airway model

30 (Comer et al, 200lb). There was a highly localized deposition at and near the carina both in the

31 first and second bifurcation, and deposition efficiency was much lower in the second bifurcation

1   than in the first bifurcation as demonstrated in the earlier study (Comer et al, 2000). They found

2   that deposition patterns were not much different between the sharp vs. rounded carina shape at

3   Stokes numbers of 0.04 and 0.12. However, deposition patterns were altered significantly for

4   these particles when the bifurcation plane was rotated, suggesting that a careful consideration of

5   realistic airway morphology is important for accurate prediction of particle deposition by CFD

6   modeling.

7   Zhang et al (2000, 2001) extended the studies of Comer et al. described above and

8   investigated effects of angled inlet tube as well as asymmetric flow distribution between daughter

9   branches. The flow asymmetry caused uneven deposition between downstream daughter

10   branches. Also noted was that the absolute deposition amount was higher, but deposition

11   efficiency per se was lower in the high flow branch than in the low flow branch. The intriguing

12   relationship between flow asymmetry and deposition was in fact consistent with experimental

13   data of Kim et al. (1999), indicating that the CFD model could correctly simulate complicated

14   airflow and particle dynamics that may occur in the respiratory airways.

15   Most CFD models use constant inspiratory or expiratory flows for simplicity and practical

16   reasons. However, the respiratory airflow is cyclic, and such flow characteristics cannot be fully

17   described by constant flows. Recent studies of Zhang et al. (2002) investigated particle

18   deposition in a triple bifurcation airway model under cyclic flow conditions mimicking resting

19   and light activity breathing. Deposition dose was obtained for every mm square area. They

20   found that deposition patterns were similar to those obtained with constant flows. However,

21   deposition efficiencies were greater with the cyclic flows than constant flows, and the difference

22   could be as high as 50% for $0.02 <$ mean Stk < 0.12 during normal breathing. The CFD results

23   are qualitatively comparable to experimental data (Kim et al, 1991) that showed about 25%

24   increase in deposition with cyclic flows. With further improvement of airway morphology and

25   computational scheme, CFD modeling could be a valuable tool for exploring the microdosimetry

26   in the airway structure.

27   Current CFD models of the acinar region are limited due to the complex and dynamic

28   nature of the gas exchange region. Flow simulation in a linearly increasing volume of a spherical

29   truncated two-dimensional alveolus model show distinct velocity maxima in the alveolar ducts

30   close to the entrance and exit points of the alveolus and a radial velocity profile in the interior

31   space of the alveolus (Tsuda et al., 1996). This is in contrast to simulations based on a rigid

1   alveolus (Tsuda, 1994a,b) and suggests that a realistic simulation of the flow pattern in the acinar

2   region should involve application of time-dependent methods with moving boundary conditions.

3   Nonuniform deposition patterns, with higher deposition near the alveolar entrance ring, have

4   been predicted using numerical models (Tsuda, 1994a,b, 1996).

5   Recent studies of Chantal (2001) examined aerosol transport and deposition in 6-generation

6   alveolated ducts using 2-D computer simulation. Particle trajectories and deposition patterns

7   were obtained for one complete breathing cycle (2 s inspiration and 2 s expiration). There were

8   large non-uniformities in deposition between generations, between ducts of a given generation,

9   and within each alveolated duct, suggesting that local deposition dose can be much greater than

10   the mean acinar dose.

11

12

6.7 SUMMARY AND CONCLUSIONS

14   An understanding of biological effects of inhaled particulate matter and underlying

15   mechanisms of action requires knowledge of the dosimetry of such material. This is because the

16   dose of particles delivered to a target site or sites of concern, rather than the actual exposure

17   concentration, is the proximal cause of the biological response. Such information is also critical

18   for extrapolation of effects found in controlled exposure studies of animals to those observed in

19   human clinical studies and, also, for relating effects in potentially susceptible persons to those in

20   normal, healthy persons. Dosimetry involves delineation of the processes of particle deposition,

21   translocation, and clearance. While the current understanding of basic mechanisms of particle

22   dosimetry, clearance, and retention has not changed since the 1996 PM ACQD (U.S.

23   Environmental Protection Agency, 1996), additional information has become available on the

24   role of certain biological determinants of these processes, such as gender and age; and there has

25   been an expansion of previous knowledge about the relationship between regional deposition and

26   translocation in regard to specific particle size ranges of significance to ambient particulate

27   exposure scenarios. There also has been significant improvement in the mathematical and CFD

28   modeling of particle dosimetry in the respiratory tract of humans. Although the models have

29   become more sophisticated and versatile, validation of the models is still needed.

30   One of the areas that has improved since the 1996 PM ACQD is consideration of specific

31   and relevant ambient size particle ranges in deposition studies. One such size mode is the

1   ultrafine. While further information on respiratory deposition for this size mode is still needed,

2   there has been an improvement in the understanding of total deposition as a function of particle

3   size and breathing pattern and of certain aspects of regional deposition of ultrafine particles.

4   This new information indicates that the ET region, especially the nasal passages, is a very

5   efficient "filter" for these particles, reducing the amount which would be available for deposition

6   in the TB and A regions of the respiratory tract. Within the thoracic region, the deposition

7   distribution of ultrafine particles is highly skewed towards the proximal airway regions and

8   resembles that of coarse particles. In other words, deposition patterns of ultrafine particles are

9   very much like those of coarse particles. Another example involves studies which attempt to

10   evaluate the contribution of fine- and coarse-mode particles to deposition in various parts of the

11   respiratory tract, although there have been only a few of these.

12   It always has been clear that certain host factors affect deposition, and there has been

13   improvement since the 1996 PM AQCD in the understanding of some of these factors,

14   specifically gender and age. Recent information suggests that there are significant gender

15   differences in the homogeneity of deposition as well as the deposition rate, and this could affect

16   susceptibility. In regard to age, recent evaluations employed both mathematical models as well

17   as experimental studies, and most involved comparison of deposition in children compared to

18   adults. These studies generally indicate that children would receive greater doses of particles per

19   lung surface area than would adults. Unfortunately, deposition studies in another potentially

20   susceptible population, namely the elderly, are still lacking although there have been a number of

21   studies examining effects of chronic pulmonary disease on deposition. These studies confirmed

22   that significant increases in deposition in obstructed lungs could occur.

23   Once deposited on airway surfaces, particles are subjected to translocation and clearance.

24   While the general pathways of clearance have been known for years, recent information has

25   improved the understanding of translocation of particles within size ranges which may be of

26   specific concern for ambient exposures. One such size mode, as noted above, is the ultrafine;

27   and recent studies indicate that ultrafine particles can be rapidly cleared from the lungs into the

28   systemic circulation and reach extrapulmonary organs. This provides a mechanism whereby

29   inhaled particles may affect cardiovascular function, as noted in various epidemiological studies

30   (see Chapter 8).

1   As with experimental studies, the major improvements in mathematical modeling of
2   dosimetry involve evaluation of realistic size modes for ambient conditions, as well as
3   improvements in the precision of these models for more realistic depictions of respiratory tract
4   airflow patterns and detailed airway structures that may result in deposition "hot spots". These
5   improvements include more detailed evaluations of enhanced deposition at airway bifurcations,
6   use of parameters that allow determination of age differences in dosimetry, and improvement in
7   the modeling of clearance mechanisms.
8   Thus, in general, while our understanding of specific aspects of particle dosimetry has
9   improved since the 1996 PM AQCD, there are still areas in need of further evaluation. These
10   areas of research include dosimetry in susceptible humans, better models for extrapolation
11   between animals used in inhalation studies and humans, and better understanding of differences
12   in the manner in which particles of different and relevant ambient size modes are handled
13   following deposition. This latter research need is important for determining the potential of
14   various particle types to exert effects systemically, rather than just locally within the respiratory
15   tract.

REFERENCES

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

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

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

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

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

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

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

Asgharian, B.; Miller, F. J.; Subramaniam, R. P. (1999) Dosimetry software to predict particle deposition in humans and rats. CIIT Activities 19(3). Available: http://www.ciit.org/ACT99/ACTIVITIESMAR99/mar99.html [19 December, 2001].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Harmsen, A. G.; Muggenburg, B. A.; Snipes, M. B.; Bice, D. E. (1985) The role of macrophages in particle translocation from lungs to lymph nodes. Science (Washington, DC) 230: 1277-1280.

Heistracher, T.; Hofmann, W. (1995) Physiologically realistic models of bronchial airway bifurcation. J. Aerosol Sci. 26: 497-509.

Heistracher, T.; Hofmann, W. (1997) Flow and deposition patterns in successive airway bifurcations. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl.): 537-542.

Henshaw, D. L.; Fews, A. P. (1984) The microdistribution of alpha emitting particles in the human lung. In: Smith, H.; Gerber, G., eds. Lung modelling for inhalation of radioactive materials: proceedings of a meeting jointly organized by the Commission of the European Communities and the National Radiological Protection Board; March; Oxford, United Kingdom. Luxembourg: Commission of the European Communities; pp. 199-218; report no. EUR 9384 EN.

Heyder, J.; Rudolf, G. (1977) Deposition of aerosol particles in the human nose. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 1; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 107-126.

Hiller, F. C. (1991) Health implications of hygroscopic particle growth in the human respiratory tract. J. Aerosol Med. 4: 1-23.

Hofmann, W.; Bergmann, R. (1998) Predictions of particle deposition patterns in human and rat airways. Inhalation Toxicol. 10: 557-583.

Hofmann, W.; Martonen, T. B.; Graham, R. C. (1989a) Predicted deposition of nonhygroscopic aerosols in the human lung as a function of subject age. J. Aerosol Med. 2: 49-68.

Hofmann, W.; Koblinger, L.; Martonen, T. B. (1989b) Structural differences between human and rat lungs: implications for Monte Carlo modeling of aerosol deposition. In: Mahaffey, J. A., ed. 26th Hanford life sciences symposium, modeling for scaling to man: biology, dosimetry, and response. Health Phys. 57(suppl. 1): 41-47.

Hofmann, W.; Balásházy, I.; Heistracher, T.; Koblinger, L. (1996) The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. Aerosol Sci. Technol. 25: 305-327.

Hofmann, W.; Bergmann, R.; Koblinger, L. (1999) Characterization of local particle deposition patterns in human and rat lungs by different morphometric parameters. J. Aerosol Sci. 30: 651-667.

Hofmann, W.; Asgharian, B.; Bergmann, R.; Anjilvel, S.; Miller, F. J. (2000) The effect of heterogeneity of lung structure on particle deposition in the rat lung. Toxicol. Sci. 53: 430-437.

Hsieh, T. H.; Yu, C. P. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhalation Toxicol. 10: 121-130.

Huchon, G. J.; Montgomery, A. B.; Lipavsky, A.; Hoeffel, J. M.; Murray, J. F. (1987) Respiratory clearance of aerosolized radioactive solutes of varying molecular weight. J. Nucl. Med. 28: 894-902.

International Commission on Radiological Protection. (1960) Report of Committee II on permissible dose for internal radiation (1959). Health Phys. 3.

International Commission on Radiological Protection. (1979) Limits for intakes of radionuclides by workers. Oxford, United Kingdom: Pergamon Press; ICRP publication 30, part 1.

International Commission on Radiological Protection. (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, nos. 1-3).

Jaques, P. A.; Kim, C. S. (2000) Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhalation Toxicol. 12: 715-731.

John, J.; Wollmer, P.; Dahlbäck, M.; Luts, A.; Jonson, B. (1994) Tidal volume and alveolar clearance of insoluble particles. J. Appl. Physiol. 76: 584-588.

Katz, I. M. (2001) Computer modeling of fluid dynamics and particle motion in the larynx and trachea. In: Martonen, T. B., ed. Medical Applications of Computer Modeling: The Respiratory System. Boston, MA: WIT Press, pp. 47-63.

Katz, I. M.; Martonen, T. B. (1996) Three-dimensional fluid particle trajectories in the human larynx and trachea. J. Aerosol Med. 9: 513-20.

Katz, I. M., Martonen, T. B., and Flaa, W. (1997) Three-dimensional computational study of inspiratory aerosol flow through the larynx: the effect of glottal aperture modulation. J. Aerosol Sci. 28: 1073-83.

Katz, I. M.; Davis, B. M.; Martonen, T. B. (1999) A numerical study of particle motion within the human larynx and trachea. J. Aerosol Sci. 30: 173-183.

Kesavanathan, J.; Swift, D. L. (1998) Human nasal passage particle deposition: the effect of particle size, flow rate, and anatomical factors. Aerosol Sci. Technol. 28: 457-463.

Keyhani, K.; Scherer, P. W.; Mozell, M. M. (1995) Numerical simulation of airflow in the human nasal cavity. J. Biomech. Eng. 117: 429-41.

Kim, C. S. (1989) Aerosol deposition in the lung with obstructed airways. J. Aerosol Med. 2: 111-120.

Kim, C. S. (2000) Methods of calculating lung delivery and deposition of aerosol particles. Respir. Care 45: 695-711.

Kim, C. S.; Fisher, D. M. (1999) Deposition characteristics of aerosol particles in sequentially bifurcating airway models. Aerosol Sci. Technol. 31:198-220.

Kim, C. S.; Garcia, L. (1991) Particle deposition in cyclic bifurcating tube flow. Aerosol Sci. Technol. 14: 302-315.

Kim, C. S.; Hu, S. C. (1998) Regional deposition of inhaled particles in human lungs: comparison between men and women. J. Appl. Physiol. 84: 1834-1844.

Kim, C. S.; Iglesias, A. J. (1989) Deposition of inhaled particles in bifurcating airway models: I. inspiratory deposition. J. Aerosol Med. 2: 1-14.

Kim, C. S.; Jaques, P. A. (2000) Respiratory dose of inhaled ultrafine particles in healthy adults. Phil. Trans. Roy. Soc. London A 358: 2693-2705.

Kim, C. S.; Kang, T. C. (1997) Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am. J. Respir. Crit. Care Med. 155: 899-905.

Kim, C. S.; Iglesias, A. J.; Sackner, M. A. (1987) Mucus clearance by two-phase gas-liquid flow mechanism: Asymmetric periodic flow model. J. Appl. Physiol. 62: 959-971.

Kim, C. S.; Eldridge, M. A.; Garcia, L.; Wanner A. (1989) Aerosol deposition in the lung with asymmetric airways obstruction: in vivo observation. J. Appl. Physiol. 67: 2579-2585.

Kim, C. S.; Hu, S. C.; DeWitt, P.; Gerrity, T. R. (1996) Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery method. J. Appl. Physiol. 81: 2203-2213.

Kim, C. S.; Hu, S. C.; Jaques, P.; Ding, J.; DeWitt, P. (2000) Measurement of regional deposition dose of inhaled particles in the size range of 0.04-5 μ in human lungs. Presented at: PM2000: particulate matter and health--the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.

Kimbell, J. S. (2001) Computational fluid dynamics of the extrathoracic airways. In: Martonen, T. B., ed. Medical Applications of Computer Modeling: The Respiratory System. Boston, MA: WIT Press; pp. 11-45.

Kinsara, A. A.; Tompson, R. V.; Loyalka, S. K. (1993) Computational flow and aerosol concentration profiles in lung bifurcations. Health Phys. 64: 13-22.

Koblinger, L.; Hofmann, W. (1985) Analysis of human lung morphometric data for stochastic aerosol deposition calculations. Phys. Med. Biol. 30: 541-556.

Koblinger, L.; Hofmann, W. (1988) Stochastic morphological model of the rat lung. Anat. Rec. 221: 533-539.

Koch, W.; Stöber, W. (2001) A simple pulmonary retention model accounting for dissolution and macrophage-mediated removal of deposited polydisperse particles. Inhalation Toxicol. 13: 129-148.

Kohlhäufl, M.; Brand, P.; Scheuch, G.; Meyer, T. S.; Schulz, H.; Häussinger, K.; Heyder, J. (1999) Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. Am. J. Respir. Crit. Care Med. 159: 902-906.

Kreyling, W. G. (1992) Intracellular particle dissolution in alveolar macrophages. Environ. Health Perspect. 97 :121-126.

Kreyling, W. G.; Blanchard, J. D.; Godleski, J. J.; Haeussermann, S.; Heyder, J.; Hutzler, P.; Schulz, H.; Sweeney, T. D.; Takenaka, S.; Ziesenis, A. (1999) Anatomic localization of 24- and 96-h particle retention in canine airways. J. Appl. Physiol. 87: 269-284.

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

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

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

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

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

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

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

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

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

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

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

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

Li, W.; Perzl, M.; Heyder, J.; Langer, R.; Brain, J. D.; Englmeier, K. H.; Niven, R. W.; Edwards, D. A. (1996) Aerodynamic and aerosol particle deaggregation phenomena in model oral-pharyngeal cavities. J. Aerosol Sci. 27: 1269-1286.

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

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

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

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

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

Martonen, T. B.; Yang, Y.; Xue, Z. Q. (1994a) Influences of cartilagious rings on tracheobronchial fluid dynamics. Inhalation Toxicol. 6: 185-203.

Martonen, T. B.; Yang, Y.; Xue, Z. Q. (1994b) Effects of carinal ridge shapes on lung airstreams. Aerosol Sci. Technol. 21: 119-136.

Martonen, T. B.; Schroeter, J. D.; Hwang, D.; Fleming, J. S.; Conway, J. H. (2000) Human lung morphology models for particle deposition studies. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 109-121.

Martonen, T. B.; Guan, X.; Schreck, R. M. (2001a) Fluid dynamics in airway bifurcations: I. Primary flows. Inhalation Toxicol. 13: 261-79.

Martonen, T. B.; Guan, X.; Schreck, R. M. (2001b) Fluid dynamics in airway bifurcations: II. Secondary currents. Inhalation Toxicol. 13: 281-9.

Martonen, T. B.; Guan, X.; Schreck, R. M. (2001c) Fluid dynamics in airway bifurcations: III. Localized flow conditions. Inhalation Toxicol. 13: 291-305.

Matsui, H.; Randell, S. H.; Peretti, S. W.; Davis, C. W.; Boucher, R. C. (1998) Coordinated clearance of periciliary liquid and mucus from airway surfaces. J. Clin. Invest. 102: 1125-1131.

Medinsky, M. A.; Kampcik, S. J. (1985) Pulmonary retention of [^{14}C]benzo[a]pyrene in rats as influenced by the amount instilled. Toxicology 35: 327-336.

Mercer, T. T. (1967) On the role of particle size in the dissolution of lung burdens. Health Phys. 13: 1211-1221.

Miller, F. J.; Anjilvel, S.; Ménache, M. G.; Asgharian, B.; Gerrity, T. R.. (1995) Dosimetric issues relating to particulate toxicity. Inhalation Toxicol. 7: 615-632.

Morrison, D.; Skwarski, D.; Millar, A. M.; Adams, W.; MacNee, W. (1998) A comparison of three methods of measuring ^{99m}Tc-DTPA lung clearance and their repeatability. Eur. Respir. J. 11: 1141-1146.

Morrow, P. E. (1973) Alveolar clearance of aerosols. Arch. Intern. Med. 131: 101-108.

Morrow, P. E. (1977) Clearance kinetics of inhaled particles. In: Brain, J. D.; Proctor, D. F.; Reid, L. M., eds. Respiratory defense mechanisms (in two parts), part II. New York, NY: Marcel Dekker, Inc.; pp. 491-543. (Lenfant, C., ed. Lung biology in health and disease: v. 5).

Morrow, P. E. (1986) Factors determining hygroscopic aerosol deposition in airways. Physiol. Rev. 66: 330-376.

Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.

Morrow, P. E. (1994) Mechanisms and significance of "particle overload." In: Mohr, U.; Dungworth, D. L.; Mauderly, J. L.; Oberdörster, G., eds. Toxic and carcinogenic effects of solid particles in the respiratory tract: [proceedings of the 4th international inhalation symposium]; March 1993; Hannover, Germany. Washington, DC: International Life Sciences Institute Press; pp. 17-25.

Morrow, P. E.; Yu, C. P. (1993) Models of aerosol behavior in airways and alveoli. In: Morén, F.; Dolovich, M. B.; Newhouse, M. T.; Newman, S. P., eds. Aerosols in medicine: principles, diagnosis and therapy. 2nd rev. ed. Amsterdam, The Netherlands: Elsevier; pp. 157-193.

Morrow, P. E.; Gibb, F. R.; Gazioglu, K. M. (1967) A study of particulate clearance from the human lungs. Am. Rev. Respir. Dis. 96: 1209-1221.

Musante, C. J.; Martonen, T. B. (1999) Predicted deposition patterns of ambient particulate air pollutants in children's lungs under resting conditions. In: Proceedings of the third colloquium on particulate air pollution and human health; June; Durham, NC. Irvine, CA: University of California, Air Pollution Health Effects Laboratory, p. 7-15 - 7-20.

Musante, C. J.; Martonen, T. B. (2000a) Computer simulations of particle deposition in the developing human lung. J. Air Waste Manage. Assoc. 50: 1426-1432.

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

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

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

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

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

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

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

Nikula, K. J.; Vallyathan, V.; Green, F. H. Y.; Hahn, F. F. (2001) Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs. Environ. Health Perspect. 109: 311-318.

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

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

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

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

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

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

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

Peterson, B. T.; Dickerson, K. D.; James, H. L.; Miller, E. J.; McLarty, J. W.; Holiday, D. B. (1989) Comparison of three tracers for detecting lung epithelial injury in anesthetized sheep. J. Appl. Physiol. 66: 2374-2383.

Phalen, R. F.; Oldham, M. J. (2001) Methods for modeling particle deposition as a function of age. Respir. Physiol. 128: 119-130.

Pritchard, J. N.; Jefferies, S. J.; Black, A. (1986) Sex differences in the regional deposition of inhaled particles in the 2.5-7.5 μm size range. J. Aerosol Sci. 17: 385-389.

Raabe, O. G.; Al-Bayati, M. A.; Teague, S. V.; Rasolt, A. (1988) Regional deposition of inhaled monodisperse, coarse, and fine aerosol particles in small laboratory animals. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 53-63.

Radford, E. P.; Martell, E. A. (1977) Polonium-210: lead-210 ratios as an index of residence time of insoluble particles from cigarette smoke in bronchial epithelium. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 2; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 567-581.

Rasmussen, T. R.; Andersen, A.; Pedersen, O. F. (2000) Particle deposition in the nose related to nasal cavity geometry. Rhinology 38: 102-107.

Roy, M. (1989) Lung clearance modeling on the basis of physiological and biological parameters. Health Phys. 57(suppl. 1): 255-262.

Rutland, J.; Cole, P. J. (1981) Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. Thorax 36: 654-658.

Salma, I.; Balásházy, I.; Winkler-Heil, R.; Hofmann, W.; Zaray, G. (2002) Effect of particle mass size distribution on the deposition of aerosols in the human respiratory system. J. Aerosol Sci. 33: 119-132.

Sarangapani, R.; Wexler, A. S. (2000) Modeling particle deposition in extrathoracic airways. Aerosol Sci. Technol. 32: 72-89.

Scheuch, G.; Stahlhofen, W. (1988) Particle deposition of inhaled aerosol boluses in the upper human airways. J. Aerosol Med. 1: 29-36.

Scheuch, G.; Philipson, K.; Falk, R.; Svartengren, M.; Stahlhofen, W.; Camner, P. (1995) Retention of particles inhaled in boli with and without induced bronchoconstriction. Exp. Lung Res. 21: 901-916.

Schlesinger, R. B. (1985) Clearance from the respiratory tract. Fundam. Appl. Toxicol. 5: 435-450.

Schlesinger, R. B. (1988) Biological disposition of airborne particles: basic principles and application to vehicular emissions. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 239-298.

Schlesinger, R. B. (1989) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corp.; pp. 163-192.

Schlesinger, R. B. (1995) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. 2nd ed. Washington, DC: Taylor & Francis; pp. 191-224.

Schlesinger, R. B.; Ben-Jebria, A.; Dahl, A. R.; Snipes, M. B.; Ultman, J. (1997) Disposition of inhaled toxicants. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press; pp. 493-550.

Schroter, R. C.; Sudlow, M. F. (1969) Flow patterns in models of the human bronchial airways. Respir. Physiol. 7: 341-55.

Segal, R. A.; Guan, X.; Shearer, M; Martonen, T. B. (2000a) Mathematical model of airflow in the lungs of children I: effects of tumor sizes and locations. J. Theor. Med. 2:199-213.

Segal, R. A.; Martonen, T. B.; Kim, C. S. (2000b) Comparison of computer simulations to total lung deposition to human subject data in healthy test subjects. J. Air Waste Manage. Assoc. 50: 1262-1268.

Smaldone, G. C.; Perry, R. J.; Bennett, W. D.; Messina, M. S.; Zwang, J.; Ilowite, J. (1988) Interpretation of "24 hour lung retention" in studies of mucociliary clearance. J. Aerosol Med. 1: 11-20.

Snipes, M. B. (1989) Long-term retention and clearance of particles inhaled by mammalian species. CRC Crit. Rev. Toxicol. 20: 175-211.

Snipes, M. B.; Clem, M. F. (1981) Retention of microspheres in the rat lung after intratracheal instillation. Environ. Res. 24: 33-41.

Snipes, M. B.; McClellan, R. O.; Mauderly, J. L.; Wolff, R. K. (1989) Retention patterns for inhaled particles in the lung: comparisons between laboratory animals and humans for chronic exposures. Health Phys. 57(suppl. 1): 69-78.

Snipes, M. B.; James, A. C.; Jarabek, A. M. (1997) The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. Appl. Occup. Environ. Hyg. 12: 547-554.

Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G.; Philipson, K. (1986a) Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: Aerosols: formation and reactivity, proceedings of the second international aerosol conference; September; Berlin, Federal Republic of Germany. Oxford, United Kingdom: Pergamon Press; pp. 192-196.

Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G. (1986b) Measurement of lung clearance with pulses of radioactively-labelled aerosols. J. Aerosol Sci. 17: 333-336.

Stanley, P. J.; Wilson, R.; Greenstone, M. A.; Mackay, I. S.; Cole, P. J. (1985) Abnormal nasal mucociliary clearance in patients with rhinitis and its relationship to concomitant chest disease. Br. J. Dis. Chest 79: 77-82.

Stapleton, K. W.; Guentsch, E.; Hoskinson, M. K.; Finlay, W. H. (2000) On the suitability of κ-ε turbulence modeling for aerosol deposition in the mouth and throat: a comparison with experiment. J. Aerosol Sci. 31: 739-749.

Stöber, W.; Morrow, P. E.; Koch, W.; Morawietz, G. (1994) Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J. Aerosol Sci. 25: 975-1002.

Strom, K. A.; Chan, T. L.; Johnson, J. T. (1988) Pulmonary retention of inhaled submicron particles in rats: diesel exhaust exposures and lung retention model. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 645-657.

Suarez, S.; Kazantseva, M.; Bhat, M.; Costa, D.; Hickey, A. J. (2001) The influence of suspension nebulization or instillation on particle uptake by guinez pig alveolar macrophages. Inhalation Toxicol. 13: 773-788.

Subramaniam, R. P.; Richardson, R. B.; Morgan, K. T.; Guilmette, R. A.; Kimbell, J. S. (1998) Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. Inhalation Toxicol. 10: 91-120.

Subramaniam, R. P.; Asgharian, B.; Leendert, V.; Cassee, F. R.; Freijer, J. I.; Miller, F. J.; Rombout, P. J. A. (1999) A software package for multiple-path modeling of particulate matter deposition in human and rat lungs. In: Phalen, R.; Bell, Y., eds. Proceedings of Third Colloquium on Particulate Air Pollution and Human Health. APHEL report no. 99-01, pp. 7.21-7.30. Irvine, CA: Air Pollution Health Effects Laboratory, University of California.

Svartengren, K.; Lindestad, P.; Svartengren, M.; Philipson, K.; Bylin, G.; Camner, P. (1995) Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. Am. J. Respir. Crit. Care Med. 152: 32-37.

Svartengren, K.; Philipson, K.; Svartengren, M.; Anderson, M.; Camner, P. (1996a) Tracheobronchial deposition and clearance in small airways in asthmatic subjects. Eur. Respir. J. 9: 1123-1129.

Svartengren, K.; Ericsson, C. H.; Svartengren, M.; Mossberg, B.; Philipson, K.; Camner, P. (1996b) Deposition and clearance in large and small airways in chronic bronchitis. Exp. Lung Res. 22: 555-576.

Svartengren, K.; Philipson, K.; Svartengren, M.; Camner, P. (1998) Effect of adrenergic stimulation on clearance from small ciliated airways in healthy subjects. Exp. Lung Res. 24: 149-158.

Svartengren, M.; Svartengren, K.; Aghaie, F.; Philipson, K.; Camner, P. (1999) Lung deposition and extremely slow inhalations of particles. Limited effect of induced airway obstruction. Exp. Lung Res. 25: 353-366.

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

Takahashi, S.; Asaho, S.; Kubota, Y.; Sato, H.; Matsuoka, O. (1987) Distribution of [198]Au and [133]Ba in thoracic and cervical lymph nodes of the rat following the intratracheal instillation of [198]Au-colloid and [133]BaSO$_4$. J. Radiat. Res. 28: 227-231.

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

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

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

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

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

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

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

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

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

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

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

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

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

Xu, G. B.; Yu, C. P. (1986) Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci. Technol. 5: 349-357.

Yeates, D. B.; Aspin, M. (1978) A mathematical description of the airways of the human lungs. Respir. Physiol. 32: 91-104.

Yeates, D. B.; Aspin, N.; Levison, H.; Jones, M. T.; Bryan, A. C. (1975) Mucociliary tracheal transport rates in man. J. Appl. Physiol. 19: 487-495.

Yeates, D. B.; Pitt, B. R.; Spektor, D. M.; Karron, G. A.; Albert, R. E. (1981) Coordination of mucociliary transport in human trachea and intrapulmonary airways. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 51: 1057-1064.

Yeh, H.-C.; Schum, G. M. (1980) Models of human lung airways and their application to inhaled particle deposition. Bull. Math. Biol. 42: 461-480.

Yu, G.; Zhang, Z.; Lessmann, R. (1996) Computer simulation of the flow field and particle deposition by diffusion in a 3-D human airway bifurcation. Aerosol Sci. Technol. 25: 338-352.

Yu, G.; Zhang, Z.; Lessmann, R. (1998) Fluid flow and particle diffusion in the human upper respiratory system. Aerosol Sci. Technol. 28: 146-158.

Zhang, Z.; Martonen, T. (1997) Deposition of ultrafine aerosols in human tracheobronchial airways. Inhalation Toxicol. 9: 99-110.

Zhang, L.; Asgharian, B.; Anjilvel, S. (1997) Inertial deposition of particles in the human upper airway bifurcations. Aerosol Sci. Tech. 26: 97-110.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2000) Effects of asymmetric branch flow rates on aerosol deposition in bifurcating airways. J. Med. Eng. Technol. 24: 192-202.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2001) Effects of curved inlet tube on air flow and particle deposition in bifurcating lung models. J. Biomechanics 34: 659-669.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2002) Cyclic micron-size particle inhalation and deposition in a triple bifurcation lung airway model. J. Aerosol Sci. 33: 257-281.

7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS

7.1 INTRODUCTION

Toxicological research on ambient particulate matter (PM) is used to address several related questions, including (1) does exposure to PM at relevant ambient concentrations cause toxicological effects, (2) what mechanisms may be involved in the toxicological response to PM exposure, (3) what factors affect individual or subpopulation susceptibility to the effects of PM exposure, (4) what characteristics of PM (e.g., size, composition) contribute to the observed toxicity, and (5) what are the combined effects of PM and gaseous co-pollutants in producing toxic responses? A variety of research approaches are used to address these questions, including studies of human volunteers exposed to PM under controlled conditions; in vivo studies of laboratory animals such as nonhuman primates, dogs and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. Similarly, a variety of exposure conditions are employed, including whole body and nose-only inhalation exposures to laboratory generated PM or concentrated ambient PM, tracheal or pulmonary instillation, nasal or nasopharyngeal instillation, and in vitro exposure to test materials in solution or suspension. The various research approaches are targeted to test hypotheses and, ultimately, provide a scientific basis for an improved understanding of the role of PM in producing the health effects identified by epidemiological studies.

Because of the sparsity of toxicological data on ambient PM at the time the previous PM Air Quality Criteria Document or "PM AQCD" (U.S. Environmental Protection Agency, 1996a) was completed, the discussion of respiratory effects of PM was organized into specific chemical components of ambient PM or model "surrogate" particles (e.g., acid aerosols, metals, ultrafine particles, bioaerosols, "other particle matter"). In this chapter, the conclusions of the 1996 PM AQCD are summarized for each of these components. Since completion of the previous document, there are many new studies demonstrating the potentially toxic effects of combustion-related particles. The main reason for this increased interest in combustion particles is that these

1   particles, along with the secondary aerosols that they form, are typically the dominant sources

2   represented in the fine fraction of ambient PM.

3   This chapter is organized as follows. The respiratory effects of specific components of

4   ambient PM or surrogate particles delivered by in vivo exposures of both humans and laboratory

5   animals are discussed first (Section 7.2), followed by cardiovascular and systemic effects of

6   particles (Section 7.3) and effects in laboratory animal models that mimic human disease

7   (Section 7.4). The in vitro exposure studies are discussed next (Section 7.5) because they

8   provide valuable information on potential hazardous constituents and mechanisms of PM injury.

9   The remaining section on exposure studies examines the health effects of mixtures of ambient

10   PM or PM surrogates with gaseous pollutants (Section 7.6). This organization provides the

11   underlying data for evaluation in the final section of this chapter (Section 7.7), but it may fail to

12   adequately convey the extensive and intricate linkages among the pulmonary, cardiac, and

13   nervous systems, all of which may be involved individually and in concert to represent the effects

14   of exposure to PM.

15

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17   **7.2 RESPIRATORY EFFECTS OF PARTICULATE MATTER IN**
18   **HEALTHY HUMANS AND LABORATORY ANIMALS: IN VIVO**
19   **EXPOSURES**

20   The following sections assess the respiratory effects of controlled human exposure to

21   various types of PM and also review and evaluate controlled laboratory animal toxicology

22   studies. A discussion of related in vitro studies using animal or human respiratory cells can be

23   found in Section 7.5. The discussion focuses on studies published since completion of the

24   previous 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a).

25   The biological responses occurring in the respiratory tract following controlled PM

26   inhalation include changes in pulmonary inflammation and systemic effects resulting from direct

27   effects on lung tissue. The observed responses may be dependent on the physicochemical

28   characteristics of the PM, the exposure, and the health status of the host. Many of the responses

29   are usually seen only at the higher concentrations characteristic of occupational and laboratory

30   animal exposures and not at (typically much lower) ambient particle concentrations. Moreover,

31   there are substantial differences in the inhalability and deposition profiles of PM in humans and

1   rodents (see Chapter 6 for details). Observed responses and dose-response relationships also are

2   very dependent on the specific biological response being measured.

3   *Particulate matter* is a broad term that encompasses a myriad of physical and chemical

4   species, some of which have been investigated in controlled laboratory animal or human studies

5   (see Table 7-1). However, a full discussion of all types of particles that have been studied is

6   beyond the scope of this chapter. Thus, specific criteria were used to select topics for

7   presentation. High priority was placed on studies that may (1) elucidate health effects of major

8   common constituents of ambient PM or (2) contribute to enhanced understanding of the

9   epidemiological studies. Most studies have been designed to address the question of biologic

10   plausibility, rather than providing dose-response or risk assessment quantification.

11   Diesel particulate matter (DPM) generally fits the criteria; however, because it is described

12   in other documents in great detail (U. S. Environmental Protection Agency, 1999; Health Effects

13   Institute, 1995), it is not covered extensively in this chapter. Particles with high inherent toxicity,

14   such as silica, that are of concern primarily because of occupational exposure, are excluded from

15   this chapter and are discussed in detail in other documents and reports (U.S. Environmental

16   Protection Agency, 1996b; Gift and Faust, 1997; Lippmann, 2000).

17   Most of the laboratory animal studies summarized here have used high particulate mass

18   concentrations administered by inhalation or by intratracheal instillation. The studies have used

19   doses that are generally quite high when compared to ambient levels, even when laboratory

20   animal-to-human dosimetric differences are considered. These high doses are necessary,

21   however, in laboratory animal studies that must explore potentially toxic effects using numbers

22   of subjects (animals) that are magnitudes fewer than those used in epidemiology studies. More

23   research on particle dose extrapolation is needed, therefore, to determine species differences and

24   the importance of exercise and other factors influencing particle deposition in humans that

25   together can account for a 50-fold or more difference in dose.

26   As mentioned earlier, the data available in the previous 1996 PM AQCD were from studies

27   that investigated the respiratory effects of specific components of ambient PM or surrogate

28   particles such as sulfuric acid droplets. More recently, pulmonary effects of controlled exposures

29   to ambient PM have been investigated by the use of particles collected from emission bag room

30   or ambient samplers (e.g., impactors; diffusion denuders) and by the use of aerosol concentrators

31   (e.g., Sioutas et al., 1995a,b, 2000; Gordon et al., 1998; Chang et al., 2000, Kim et al., 2000a,b).

TABLE 7-1. TYPES OF PARTICULATE MATTER USED IN TOXICOLOGICAL STUDIES

Source category	Particle[a]	Source[b]	Label/Date[c]	Description	Reference[d]
Concentrated Ambient Particles					
ambient	CAPs	New York, NY		Gerber concentrator; 0.2 to 1.2 μm MMAD; σg = 0.2 to 3.9	Gordon et al. (1998; 2000)
ambient	CAPs	Boston, MA		Harvard concentrator; 0.2 to 0.3 μm MMAD; σg = 2.9	Goldsmith et al. (1998); Clarke et al. (1999; 2000a,b)
ambient	CAPs	Boston, MA	1997 1998	Harvard concentrator; 0.23 to 0.34 μm MMAD; σg = 0.2 to 2.9	Godleski et al. (2000)
ambient	CAPs	Chapel Hill, NC; Research Triangle Park, NC	1997 1998	Harvard concentrator; 0.65 μm MMAD; σg = 2.35	Ghio et al. (2000a); Kodavanti et al. (2000a)
ambient	CAPs	Los Angeles, CA		Harvard concentrator; $PM_{2.5}$	Gong et al., (2000)
Ambient Particulate Matter Extracts					
ambient (aqueous extracts)	urban PM (StL)	St. Louis, MO	SRM 1648		Dong et al., (1996); Becker and Soukup (1998)
ambient (aqueous extracts)	urban PM (Ott)	Ottawa, ONT	EHC-93; 1993	videlon filter samples, mechanically sieved (36, 56, 80, 100, 300 μm), and stored at -80 °C	Vincent et al. (1997; 2001)
ambient (aqueous extracts)	urban PM (Dus)	Dusseldorf, Germany			Costa and Dreher (1997)
ambient (aqueous extracts)	urban PM	Terni, Italy			Fabiani et al. (1997)
ambient (aqueous extracts)	urban PM (WDC)	Washington, DC	SRM 1649		Becker and Soukup (1998)
ambient (aqueous extracts)	urban PM	Provo, UT	1981, 1982	TSP collected on glass-fiber filters, suspended in aqueous medium, centrifuged, lyophilized, and resuspended in saline.	Kennedy et al. (1998); Ghio et al. (1999a,b)
ambient (aqueous extracts)	urban PM	Provo, UT	1986, 1987, 1988	TSP and PM_{10} collected on glass hi-vol filters, suspended, centrifuged, lyophilized, and resuspended in saline.	Dye et al., (2001); Ghio and Devlin, (2001)
ambient (aqueous extracts)	urban CB & UCB	Edinburgh, UK			Li et al. (1996; 1997)
ambient (aqueous extracts)	urban dust	NIST; Gaithersburg, MD			

TABLE 7-1 (cont'd). TYPES OF PARTICULATE MATTER USED IN TOXICOLOGICAL STUDIES

Source category	Particle[a]	Source[b]	Label/Date[c]	Description	Reference[d]
Complex Combustion-Related Particulate Matter					
stationary	coal fly ash (CFA)	U.S. power plants			
stationary	oil fly ash (OFA)	Niagra power plant			
stationary	residual oil fly ash (ROFA)	variable			Watkinson et al. (1998; 2000a,b); Campen et al. (2000); Muggenburg et al. (2000)
residential	domestic oil fly ash (DOFA)	home oil-burning furnace			
residential	wood stove	Durham, NC			
mobile	diesel exhaust particles (DEP)				
mobile	diesel particulate matter (DPM)				
Laboratory-Derived Surrogate Particulate Matter					
ambient (simulated)	acid aerosols (e.g., H_2SO_4)			See Table 7-2	
ambient (simulated)	bioaerosols (e.g., lipopolysaccharide, LPS)			See Table 7-7	
stationary (simulated)	inorganic metal oxides (CdO, Fe_2O, MnO_2, $NiSO_4$, TiO_2, V_2O_5, ZnO)			See Table 7-3	
mobile	diesel soot	NIST; Gaithersburg, MD	SRM 1650		
natural	Mt. St. Helens ash (MSH)	Ritzville, WA			
natural	coal dust				
inorganic	carbon black (CB)				
organic	synthetic polymer microspheres (SPM)				

[a] Particle Notes:
1. See Tables 7-4, 7-5, 7-6 and 7-8 for description and additional information on studies using ambient PM and PM substitutes.
2. See Table 7-2 for description and additional information on studies using acid aerosols.
3. See Table 7-3 for description and additional information on studies using metal oxides.
4. See Table 7-7 for description and additional information on studies using ambient bioaerosols.
5. For additional information on Diesel PM (DPM) or Diesel exhaust particles (DEP), see U.S. Environmental Protection Agency (2000) and Health Effects Institute (1995).
6. UCB = fine or ultrafine urban carbon black particles.

[b] Source Notes:
1. Aerosol concentrators (e.g., Harvard; Gerber) were used to generate CAPs.
2. Particle samplers (e.g., impactors, diffusion denuders) were used to collect ambient PM.
3. NIST = National Institute of Standards and Technology.

[c] Label / Date Notes:
• SRM = standard reference material.
• EHC = Environmental Health Center in Ottawa, Canada.
• Date of particle collection, when available.

[d] Reference: Not an exhaustive list; see text for details.

1   Some ambient PM has been standardized as a reference material and compared to existing dust

2   and soot standards [e.g., National Institutes of Standards and Technology (NIST)]. Both ambient

3   PM and CAPs have been used to investigate effects in normal and compromised laboratory

4   animals and humans.

5   Particles from ambient air samplers are collected on filters or other media, stored, and

6   resuspended in an aqueous medium for use in experimental, tracheal installation, or in vitro

7   studies. The in vivo and in vitro studies discussed in this chapter have almost exclusively used

8   PM_{10} or $PM_{2.5}$ as particle size cutoffs for studying the adverse effects of ambient PM. Studying

9   only particles less than a certain size is justified based upon earlier interests in setting standards

10 for PM_{10} and $PM_{2.5}$. In addition, the collection of these size fractions is made easier by the

11 widespread availability of ambient sampling equipment for PM_{10} and $PM_{2.5}$. Unfortunately, the

12 study of other important size fractions, such as the coarse fraction ($PM_{10-2.5}$) and $PM_{1.0}$ has been

13 largely ignored and little toxicology data are available to specifically address these potentially

14 important particle sizes. Similarly, organic compounds make up 20 to 60% of the dry fine

15 particle mass of ambient PM (Chapter 3, Section 3.2), yet very little research has addressed the

16 mechanisms by which this organic fraction contributes to the adverse effects associated with

17 acute exposure to PM. The potential contribution of organics in mutagenesis and carcinogenesis

18 has been studied, but these findings are not discussed within the context of this chapter which is

19 focused on understanding the epidemiologic evidence of increased cardiopulmonary morbidity

20 and mortality associated with acute exposure to ambient PM.

21   Particle concentrators provide a technique for exposing animals or humans by inhalation to

22 concentrated ambient particles (CAPs) that are 5 to 10-fold higher than typical ambient PM

23 levels. The development of particle concentrators has permitted the study of true ambient PM

24 under controlled conditions. This strength is somewhat weakened by the inability of CAPs

25 studies to precisely control the mass concentration and day-to-day variability in ambient particle

26 composition. Nonetheless, these studies are invaluable in the attempt to understand the

27 biological mechanisms responsible for the cardiopulmonary response to inhaled PM. Because

28 the composition of concentrated ambient PM varies in both time and location, a thorough

29 physical-chemical characterization is necessary to compare results among studies or even among

30 exposures within studies or to link particle composition to effect.

31

7.2.1 Ambient Combustion-Related and Surrogate Particulate Matter

In vivo toxicology studies utilizing inhalation exposure as a technique for measuring the respiratory effects of ambient particles in humans and laboratory animals have been conducted with CAPs (see Table 1) and with DPM. The majority of the in vivo exposures have utilized intratracheal instillation techniques. Discussions on the pros and cons of this technique in comparison to inhalation are covered in Chapter 6 (Section 6.5), and these issues have also been reviewed elsewhere (Driscoll et al., 2000; Oberdörster et al., 1997; Osier and Oberdörster, 1997). In most of the studies, PM samples were collected on filters, resuspended in a vehicle (usually saline), and a small volume of the suspension was instilled intratracheally into the animals. The physiochemical characteristics of PM may be altered by deposition on a filter and resuspension in an aqueous medium. In addition, the doses used in these instillation studies are generally high compared to ambient concentrations, even when laboratory animal-to-human dosimetric differences are considered. Therefore, in terms of direct extrapolation to humans in ambient exposure scenarios, greater importance should be placed on inhalation studies. However, delivery of PM by instillation has the advantages that much less material is needed and that the delivered dose can be determined directly without extrapolating from estimates of lung deposition. Instillation studies have proven valuable in comparing the effects of different types of PM and for investigating some of the mechanisms by which particles may cause lung injury and inflammation. Tables 7-2, 7-3, and 7-4 outline studies in which various biological endpoints were measured following exposures to CAPs, ambient PM extracts, complex combustion-related PM, or laboratory-derived surrogate PM, respectively.

There were only limited data available from human studies or laboratory animal studies on ultrafine particles and even less on coarse particles at the time of the release of the previous criteria document (U.S. Environmental Protection Agency, 1996a). In vitro studies have shown that ultrafine particles have the capacity to cause injury to cells of the respiratory tract. High levels of ultrafine particles, as metal or polymer "fume," are associated with toxic respiratory responses in humans and other mammals. Such exposures are associated with cough, dyspnea, pulmonary edema, and acute inflammation. At concentrations less than 50 μg/m^3, freshly generated insoluble ultrafine PTFE fume particles can be severely toxic to the lung. However, it was not clear what role in the observed effects was played by fume gases which adhered to the particles. Newer data from controlled exposures have demonstrated that particle composition, in

TABLE 7-2. RESPIRATORY EFFECTS OF AMBIENT PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, male S-D 200-225 g, control and SO_2-treated	Concentrated ambient particles (CAPs) (Boston)	Inhalation; Harvard/EPA fine particle concentrator; animals restrained in chamber	206,733, 607 $\mu g/m^3$ for Days 1-3; 29 °C, 59% RH	0.18 μm $\sigma g = 2.9$	5 h/day for 3 days	PEF and TV increased in CAPS exposed animals. Increased protein and % neutrophils and lymphocytes in lavage fluid after CAPS exposure. Responses were greater in SO_2-bronchitis animals. No changes in LDH. No deaths occurred.	Clarke et al. (1999)
Rats, male S-D 60 days	Provo, UT, TSP filters (10 years old)	Intratracheal instillation	0.25, 1.0, 2.5, 5.0 mg of PM extract in 0.3 mL saline	N/A	24 h	Inflammation (PMN) and pulmonary injury was produced by particles collected while the steel mill was in operation	Dye et al. (2001)
Humans, healthy nonsmokers; 21 M, 3F; 26.4±2.2 yr old	Provo, UT, PM_{10} filters (10 years old)	Intrabronchial instillation	500 μg of PM extract in 10 mL saline	N/A	24 h BAL	Inflammation (PMN) and pulmonary injury was produced by particles collected while the steel mill was in operation	Ghio and Devlin (2001)
Rats, S-D 60 days	Provo, UT, TSP filters (10 years old), soluble and insoluble extracts	Intratracheal instillation	100-1000 μg of PM extract in 0.5 mL saline	N/A	24 h	Inflammation (PMN) and lavage fluid protein was greater with the soluble fraction containing more metal (Zn, Fe, Cu).	Ghio et al. (1999a)
Humans, healthy nonsmokers; 18 to 40 yr old	CAPs (Chapel Hill)	Inhalation	23.1 to 311.1 $\mu g/m^3$	0.65 μm $\sigma g = 2.35$	2 h; analysis at 18 h	Increased BAL neutrophils in both bronchial and alveolar fractions	Ghio et al. (2000a)
Mongrel dogs, some with balloon occluded LAD coronary artery n = 14	CAPs (Boston)	Inhalation via tracheostomy	69-828 $\mu g/m^3$	0.23 to 0.34 μm $\sigma g = 0.2$ to 2.9	6 h/day × 3 days	Decreased respiratory rate and increased lavage fluid neutrophils in normal dogs.	Godleski et al. (2000)
Humans, healthy; n=4, 19-41 yr old	CAPs (LA)	Inhalation	148-246 $\mu g/m^3$	$PM_{2.5}$	2 h	No significant changes in lung function, symptoms, S_aO_2, or Holter ECGs were observed.	Gong et al. (2000)
Rats, male F 344 Hamsters, male, 8-mo-old Bi TO-2	CAPs (NY)	Inhalation	132 to 919 $\mu g/m^3$	0.2 to 1.2 μm $\sigma g = 0.2$ to 3.9	1 × 3 h or 3 × 6 h	No inflammatory responses, no cell damage responses, no PFT changes.	Gordon et al. (2000)
Rats, male, 90 to 100-day-old S-D, with or without SO_2-induced bronchitis	CAPs (RTP)	Inhalation	650 $\mu g/m^3$		6 h/day × 2-3 days	No significant changes in healthy rats; increased BALF protein and neutrophil influx in bronchitic rats; responses were variable between exposure regimens.	Kodavanti et al. (2000a)
Rats, Wis (HAN strain)	Ambient PM Edinburgh, CB, CB Ultrafine (UCB)	Intratracheal instillation	50-125 μg in 0.2 mL	PM_{10} CB = (200-500 nm) UCB = 20 nm	Sacrificed at 6 h	Increased PMN, protein, and LDH following PM_{10}; greater response with ultrafine CB but not CB; decreased GSH level in BAL; free radical activity (deplete supercoil DNA); leukocytes from treated animals produced greater NO and TNF.	Li et al. (1996, 1997)

[a]See Table 1 for details

TABLE 7-3. RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Hamsters, Syrian golden, male, 90-125g	Kuwaiti oil fire particles; urban particles from St. Louis, MO	Intratracheal instillation	0.15, 0.75, and 3.75 mg/100g	Oil fire particles: <3.5 μm, 10 days of 24-h samples	Sacrificed 1 and 7 days post instillation	Increases in PMN, AM, albumin, LDH, myeloperoxidase, and β-N-acetylglucosaminidase; acute toxicity of the particles found in the smoke from the Kuwaiti oil fires is comparable to that of urban particles.	Brain et al. (1998)
Mice, female, NMRI, 28-32g	CFA CMP WC	Intratracheal instillation	CMP: 20 μg arsenic/kg, or CMP: 100 mg particles/kg, WC alone (100 mg/kg), CFA alone (100 mg/kg [i.e., 20 μg arsenic/kg]), CMP mixed with WC (CMP, 13.6 mg/kg [(i.e., 20 μg arsenic/kg]), WC (86.4 mg/kg) and $Ca_3(AsO_4)_2$ mixed with WC (20 μg arsenic/kg), WC (100 mg/kg)	N/A	1, 5, 30 days posttreatment, lavage for total protein content, inflammatory cell number and type, and TNF-α production particle retention	Mild inflammation for WC; $Ca_3(AsO_4)_2$ caused significant inflammation; CMP caused severe but transient inflammation; CFA caused persistent alveolitis; cytokine production was upregulated in WC- and $Ca_3(AsO_4)$ treated animals after 6 and 30 days, respectively; a 90% inhibition of TNF-α production still was still observed at Day 30 after administration of CMP and CFA; a significant fraction persisted (10-15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at Day 30. Suppression of TNF-α production is dependent on the slow elimination of the particles and their metal content from the lung	Broeckaert et al. (1997)
Rats, male, S-D, 60 days old	Emission source PM (ROFA, DOFA, CFA) Ambient airshed PM ROFA	Intratracheal instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 and 96 h following instillation	Increases in PMNs, albumin, LDH, PMN, and eosinophils following exposure to emission and ambient particles; induction of injury by emission and ambient PM samples is determined primarily by constituent metals and their bioavailability.	Costa and Dreher (1997)
Rats, male WISTAR Bor: WISW strain	Coal oil fly ash	Inhalation (chamber)	0, 11, 32, and 103 mg/m^3	1.9-2.6 μm σg = 1.6-1.8	6 h/day, 5days/week, 4 weeks	At the highest concentration, type II cell proliferation and mild fibrosis occurred and increased perivascular lymphocytes were seen. The main changes at the lowest concentration were particle accumulation in AM and mediastinal lymph nodes. Lymphoid hyperplasia observed at all concentrations. Effects increased with exposure duration.	Dormans et al. (1999)

TABLE 7-3 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, male, S-D, 60 days old	ROFA	Intratracheal instillation	8.33 mg/mL 0.3 mL/rat	1.95 μm MMAD	Analysis at 24 and 96 h	Increased PMNs, protein, LDH at both time points; bioavailable metals were causal constituents of pulmonary injury.	Dreher et al. (1997)
Rats, S-D, 5-day-old	ROFA	Intratracheal Instillation	500 μg/rat	1.95 μm MMAD	24h	Increased neutrophilic inflammation was inhibited by DMTU treatment, indicating role of ROS.	Dye et al. (1997)
Rats, male, S-D rats 60 days old	#6 ROFA, volcanic ash	Intratracheal Instillation	0.3, 1.7 8.3 mg/mL 8.3 mg/mL	1.95 μm σg = 2.19 1.4 μm	24 h	Plasma fibrinogen elevated after ROFA instillation but not volcanic ash	Gardner et al. (2000)
Rats, male, S-D, 5-day-old	Low S #6 ROFA, volcanic ash saline	Intratracheal Instillation	0.3, 1.7, 8.3 mg/kg BW in saline 8.3 mg/kg BW 1 mL/kg BW	1.95 μm σg = 1.95 1.4 μm	24 h	Increased WBC count in ROFA-exposed rats plasma fibrinogen increased 86% in ROFA rats at highest concentration.	Gardner et al. (2000)
Rats, male, S-D, 60 days old	Two ROFA samples R1 had 2× saline-leachable sulfate, Ni, and V and 40× Fe as R2; R2 had 31× higher Zn	Intratracheal instillation	2.5 mg in 0.3 mL	R1: 1.88 μm, MMAD R2: 2.03 μm, MMAD	Analysis at 4 days	Four of the 24 animals treated with R2 or R2s (supernatant) died; none in R1s treated animals; more AM, PMN, eosinophils protein, and LDH in R2 and R2s animals; more focal alveolar lesions, thickened alveolar septae, hyperplasia of type II cells, alveolar fibrosis in R2 and R2s animals; baseline pulmonary function and airway hyperreactivity were worse in R2 and R2s groups.	Gavett et al. (1997)
Mice, female, Balb/cJ 7-15 weeks	ROFA	Intratracheal instillation	60 μg in 50 μL (dose 3mg/kg)	< 2.5	Analysis at 1-15 days after instillation	ROFA caused increases in eosinophils, IL-4 and IL-5 and airway responsiveness in ovalbumin-sensitized and challenged mice.	Gavett et al. (1999)
Mice, female, 7-week-old Balb/cJ (16-21 g)	ROFA lo-S residual oil	Inhalation and intratracheal instillation challenge with OVA	158 ± 3 mg/m^3	PM$_{2.5}$ sample	1, 3, 8, 15 days after instillation	Increased BAL protein and LDH at 1 and 3 days but not at 15 days postexposure. Combined OVA and ROFA challenge increased all damage markers and enhanced allergen sensitization. Increased methacholine response after ROFA.	Gavett et al. (1999)
Rats, male, S-D	ROFA	Intratracheal instillation	500 μg/animal	3.6 μm	Analyzed 4 and 96 h postexposure	Ferritin and transferrin were elevated; greatest increase in ferritin, lactoferrin, transferrin occurred 24 h postexposure.	Ghio et al. (1998b)
Mice, normal and Hp, 105 days old	ROFA	Intratracheal instillation	50 μg	1.95 μm	Analysis at 24 h	Diminished lung injury (e.g., decreased lavage fluid ascorbate, protein, lactate dehydrogenase, inflammatory cells, cytokines) in Hp mice lacking transferrin; associated with increased metal storage and transport proteins.	Ghio et al. (2000b)
Mice, BALB/C, 2-day-old, sensitized to ovalbumin (OVA)	Aerosolized ROFA leachate	Nose-only inhalation	50 mg/mL	N/A	30 min	Increased airway response to methylcholine and to OVA in ROFA exposed mice; increased airway inflammation also.	Hamada et al. (1999)

TABLE 7-3 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, male, S-D, 60 days old	ROFA	Intratracheal instillation	1.0 mg in 0.5 mL saline	1.95 μm	Analysis at 24 h	Increased PMNs, protein.	Kadiiska et al. (1997)
Rats, S-D, 250 g MCT	FOFA	Inhalation	$580 \pm 110\ \mu g/m^3$	2.06 μm MMAD $\sigma g = 1.57$	6 h/day for 3 days	Death occurred only in MCT rats exposed to ROFA. Neutrophils in lavage fluid were increased significantly in MCT rats exposed to ROFA versus filtered air. MIP-2 mRNA expression in lavage cells was induced in normal animals exposed to fly ash.	Killingsworth et al. (1997)
Rats, male, S-D and F-344 (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm $\sigma g = 2.14$	Sacrificed at 24 h	Increase in neutrophils in both S-D and F-344 rats; a time-dependent increase in eosinophils occurred in S-D rats but not in F-344 rats.	Kodavanti et al. (1996)
Rats, male, S-D, WIS, and F-344 (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm $\sigma g = 2.14$	Sacrificed at 6, 24, 48, and 72 h; 1, 3, and 12 weeks	Inflammatory cell infiltration, as well as alveolar, airway, and interstitial thickening in all three rat strains; a sporadic incidence of focal alveolar fibrosis in S-D rats, but not in WIS and F-344 rats; cellular fibronectin (cF_n) mRNA isoforms EIIIA(+) were up-regulated in S-D and WIS rats but not in F-344 rats. Fn mRNA expression by macrophage, alveolar and airway epithelium, and within fibrotic areas in S-D rats; increased presence of Fn EIIIA(+) protein in the areas of fibrotic injury and basally to the airway epithelium.	Kodavanti et al. (1997a)
Rats, male, S-D, 60 days old	ROFA $Fe_2(SO_4)_3$, VSO_4, $NiSO_4$	Intratracheal instillation	8.33 mg/kg ROFA-equivalent dose of metals	1.95 μm $\sigma g = 2.14$	Analysis at 3, 24, and 96 h, postinstillation	ROFA-induced pathology lesions were as severe as those caused by Ni. Metal mixture caused less injury than ROFA or Ni alone; Fe was less pathogenic. Cytokine and adhesion molecule gene expression occurred as early as 3 h after exposure. V-induced gene expression was transient but Ni caused persistent expression and injury.	Kodavanti et al. (1997b)
Rats, male, S-D, 60 days old	10 compositionally different ROFA particles from a Boston power plant	Intratracheal instillation	0.833, 3.33, 8.3 mg/kg	1.99–2.59 μm MMAD	Sacrificed at 24 h	ROFA-induced increases in BAL protein and LDH, but not PMN, were associated with water-leachable total metal, Ni, Fe, and S; BALF neutrophilic inflammation was correlated with V but not Ni or S. Chemiluminescence signals in vitro (AM) were greatest with ROFA containing soluble V and less with Ni plus V.	Kodavanti et al. (1998a)

TABLE 7-3 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, male, S-D 60-day-old treated with MCT (60 mg/kg)	ROFA	Intratracheal instillation; Nose-only inhalation	0, 0.83, 3.3 mg/kg 15 mg/m^3	1.95 μm σg = 2.14	24-96 h 6 h/day for 3 days analysis at 0 or 18 h	Both IT and IN rats showed inflammatory responses (IL-6, MIP-2 genes upregulated). 58% of IT rats exposed to ROFA died within 96 h. No mortality occurred by inhalation. ROFA exacerbated lung lesions (edema, inflammation, alveolar thickening) and gene expression in MCT rats.	Kodavanti et al. (1999)
Rats, male, WKY and SH, 11-13 weeks old	ROFA	Nose-only Inhalation	15 mg/m^3	1.95 μm σg = 2.14	6 h/day × 3 day, analysis at 0 or 18 h	More pulmonary injury in SH rats. Increased RBCs in BALF of SH rats. ROFA increased airway reactivity to Ach in both SH and WKY rats. Increased protein, albumin, and LDH in BALF after ROFA exposure (SH>WKY). Increased oxidative stress in SH rats. SH rats failed to increase glutathione. Inflammatory cytokine gene expression increased in both SH and WKY rats.	Kodavanti et al. (2000b)
Rats, male, WKY and SH, 11-13 weeks old	ROFA VSO$_4$, NiSO$_4$, or saline	Intratracheal Instillation	3.33 mg/mL/kg 1.5 μmol kg	1.95 μm σg = 2.14	1 and 4 days; post instillation analysis at 6 or 24 h	Increased BALF protein and LDH alveotis with macrophage accumulation in alveoli; increased neutrophils in BAL. Increased pulmonary protein leakage and inflammation in SH rats. Effects of metal constituents of ROFA were strain specific; vanadium caused pulmonary injury only in WKY rats; nickel was toxic in both SH and WKY rats.	Kodavanti et al. (2001)
Rats, Brown Norway	ROFA	Intratracheal instillation	200 μg 100 μg	N/A	N/A	ROFA enhanced the response to house dust mite (HDM) antigen challenge. Eosinophil numbers, LDH, BAL protein, and IL-10 were increased with ROFA + HDM versus HDM alone.	Lambert et al. (1999)
Rats, male, S-D, 60-day-old	#6 ROFA from Florida	Intratracheal instillation	1000 μg in 0.5 ml	1.95 ± 0.18 μm	15 min to 24 h	Production of acetaldehyde increased at 2 h postinstillation.	Madden et al. (1999)
Rats, male, S-D, 60-day-old	NC ROFA; Domestic oil fly ash	Intratracheal instillation	1000 μg in 0.5 mL saline		15 min to 24 h	ROFA induced production of acetaldehyde with a peak at about 2 h. No acetaldehyde was seen in plasma at any time. DOFA increased acetaldehyde, as did V and Fe.	Madden et al. (1999)
Rats, male, S-D; 60 days old	#6 ROFA (Florida) NiSO$_4$ VSO$_4$	Intratracheal instillation	3.3 mg/ml/kg; ROFA equivalent dose of metals	1.9 μm σ$_g$ = 2.14	3 or 24 h	Inflammatory and stress responses were upregulated; the numbers of genes upregulated were correlated with metal type and ROFA	Nadadur et al. (2000); Nadadur and Kodavanti (2002)
Rats, male, S-D, 60-day-old	ROFA	Intratracheal instillation	400-1000 μg/mL	N/A	12 h post-IT	ROFA increased PGE$_2$ via cycloxygenase expression.	Samet et al. (2000)

TABLE 7-3 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, male, S-D, 60-day-old	LoS, #6 ROFA	Intratracheal instillation	500 μg in 0.5 ml saline	3.6 μm	1, 4, or 24 h	Mild and variable inflammation at 4 h; no pronounced inflammation until 24 h when there were marked increases in P-Tyr and P-MARKS.	Silbajoris et al. (2000)
Rats, male, S-D; 60-day-old; WKY and SH; cold-stressed SH, ozone-exposed SH, and MCT-treated SH	Ottawa dust, ROFA, and volcanic ash	Intratracheal instillation, nose-only inhalation	Dose: IT 0, 0.25, 1.0, and 2.5 mg/rat; INH 15 mg/m^3	1.95 μm	6 h/day for 3-day inhalation; instillation - 96 h post-IT	IT ROFA caused acute and dose-related increase in pulmonary inflammation; no effect of volcanic ash.	Watkinson et al. (2000a,b)

[a]See Table 1 for details (CFA = Coal fly ash; CMP = Copper smelter dust; WC = Tungsten carbide; MCT = Monocrotaline; DOFA = Fly ash from a domestic oil-burning furnace; Fe$_2$(SO$_4$) = Iron sulfate; V SO$_4$ = Vanadium sulfate; NiSO$_4$ = Nickel sulfate; LoS = low sulfur)

TABLE 7-4. RESPIRATORY EFFECTS OF SURROGATE PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Hamsters, Syrian golden 900 male, 900 female, 4-wks-old	Toner (carbon) TiO_2 Silica	Nose-only inhalation	1.5, 6.0, or 24 mg/m^3 40 mg/m^3 3 mg/m^3	4.0 μm 1.1 μm 1.4 μm	3, 9, 15 mo 6 h/day 5days/week	Retention increased with increased exposure. Clearance halftimes retarded (males)	Creutzenberg et al. (1998)
Mice, C57Bl/6J	PTFE TiO_2	Inhalation	PTFE: 1.25, 2.5, or 5 x 10^5 particles/cc TiO_2-F: 10 mg/m^3 NiO: 5 mg/m^3 Ni$_3$S$_2$: 0.5 mg/m^3	PTFE: 18 nm TiO_2-F: 200 nm TiO_2-D: 10 nm	30 min or 6 h/day, 5days/week, 6 mo	Effects on the epithelium caused by direct interactions with particles, not a result of macrophage-derived mediators, and suggest a more significant role in the overall pulmonary response than previously suspected; type II cell growth factor production may be significant in the pathogenesis of pulmonary fibrosis.	Finkelstein et al. (1997)
Rats, male, F-344 200-230 g	PTFE Fumes	Whole body inhalation	1, 2.5, or 5 × 10^5 particles/cm3	18 nm	15 min, analysis 4 h postexposure	Increased PMN, mRNA of MnSOD and MT, IL-1α, IL-1β, IL-6, MIP-2, TNF-α mRNA of MT and IL-6 expressed around all airways and interstitial regions; PMN expressed IL-6, MT, and TNF-α; AM and epithelial cells were actively involved.	Johnston et al. (1996)
Mice, male, C57BL/6J, 8 weeks and 8-mo-old	PTFE Fumes	Whole body inhalation	1, 2.5, or 5 × 10^5 particles/cm3	18 nm	30-min exposure, analysis 6 h following exposure	Increased PMN, lymphocytes, and protein levels in old mice over young mice; increased TNF-α mRNA in old mice over young mice; no difference in LDH and β-Glucuronidase.	Johnston et al. (1998)
Rats, male, S-D, MCT-treated	Fluorescent microspheres	Inhalation	3.85 ± 0.81 mg/m^3	1.38 ± 0.10 μm σ_g = 1.8 ± 0.28	3 h/day × 3 days	Monocrotaline-treated animals contained fewer microspheres in their macrophages, probably because of impaired chemotaxis.	Madl et al. (1998)
Rats, male, S-D (200g)	Diesel, SiO_2, carbon black	Intratracheal instillation	1 mg in 0.4 mL.	DEP Collected as TSP - disaggregated in solution by sonication (20 nm); SiO_2 (7 nm); carbon black	Necropsy at 2, 7, 21, 42, and 84 days postinstillation	Amorphous SiO_2 increased permeability, and neutrophillic inflammation. Carbon black and DEP translocated to interstitum and lymph nodes by 12 weeks.	Murphy et al. (1998)
Mice, male, Swiss-Webster, 6-8 weeks old (A/J, AKR/J, B6C3F1/J, BALB/cJ, C3H/HeJ-C3, C3HeOuJ, CSTBL/6J-B6, SJL/J, SWR/J, 129/J) strains raised in a pathogen free laboratory	Carbon black Regal 660 Carbon-associated $SO_4^=$	Nose only inhalation	10 mg/m^3 285 μg/m^3	0.29 μm ± 2.7 μm	4 h	Differences in inflammatory responses (PMN) across strains. Appears to be genetic component to the susceptibility.	Ohtsuka et al. 2000a,b

[a]See Table 1 for details (PTFE = polytetrafluoroethylene; TiO_2 = titanium oxide; SiO_2 = silicon dioxide)

1   addition to particle size, may be responsible for the adverse health effects associated with

2   ambient PM exposures.

3   Toxicologic studies of other particulate matter species also were discussed in the previous

4   criteria document (U.S. Environmental Protection Agency, 1996a). These studies included

5   exposures to fly ash, volcanic ash, coal dust, carbon black, and miscellaneous other particles,

6   either alone or in mixture. Some of the particles discussed were considered to be models of

7   "nuisance" or "inert" dusts (i.e., those having low intrinsic toxicity) and were used in instillation

8   studies to delineate nonspecific particle effects from effects of known toxicants. A number of

9   studies on "other PM" examined effects of up to 50,000 μg/m^3 of respirable particles with

10   inherently low toxicity. Although there was no mortality, some mild pulmonary function

11   changes after exposure to 5,000 to 10,000 μg/m^3 of inert particles were observed in rats and

12   guinea pigs. Lung morphology studies revealed focal inflammatory responses, some epithelial

13   hyperplasia, and fibrotic responses after exposure to >5,000 μg/m^3. Changes in macrophage

14   clearance after exposure to >10,000 μg/m^3 were equivocal (no host defense effects). In studies of

15   mixtures of particles and other pollutants, effects were variable depending on the toxicity of the

16   associated pollutant. In humans, co-exposure to carbon particles appeared to increase responses

17   to formaldehyde but not to acid aerosol. None of the "other" particles mentioned above are

18   present in ambient air in more than trace quantities. Thus, it was concluded that the relevance of

19   any of these studies to standard setting for ambient PM may be extremely limited (see Chapter 6,

20   Section 4, *Particle Overload*).

21

22   **7.2.1.1 Ambient Particulate Matter**

23   Studies that examined the acute effects of intratracheal instillation of ambient PM obtained

24   from specific ambient sources have shown clearly that PM can cause lung inflammation and

25   injury. Costa and Dreher (1997) showed that instillation of relatively high concentrations of PM

26   samples from three emission sources (two oil and one coal fly ash) and four ambient airsheds (St.

27   Louis, MO; Washington, DC; Dusseldorf, Germany; and Ottawa, Canada) resulted in increases in

28   lung polymorphonuclear leucocytes (PMNs) and eosinophils in rats 24 h after instillation.

29   Biomarkers of permeability (total protein and albumin) and cellular injury (LDH) also were

30   increased. This study demonstrated that the lung dose of bioavailable transition metal, not

31   instilled PM mass, was the primary determinant of the acute inflammatory response. Kennedy et

1   al. (1998) reported a similar dose-dependent inflammation (i.e., increase in protein and PMN in

2   lavage fluid, proliferation of bronchiolar epithelium, and intraalveolar hemorrhage) in rats

3   instilled with water-extracted particles (TSP) collected in Provo, UT. This study also indicated

4   that the metal constituent, in this case PM-associated Cu, was a plausible cause of the outcome.

5   Likewise, instillation of ambient PM_{10} collected in Edinburgh, Scotland, also caused pulmonary

6   injury and inflammation in rats (Li et al., 1996, 1997). Brain et al. (1998) examined the effects

7   of instillation of particles that resulted from the Kuwaiti oil fires in 1991 compared to urban

8   particulate matter collected in St. Louis (NIST SRM 1648, collected in a bag house in early

9   1980s) and showed that on an equal mass basis, the acute toxicity of the Kuwaiti oil fire particles

10   was similar to that of urban particles collected in the United States.

11   Toxicological studies of ambient PM collected around Provo, UT (Utah Valley) in the late

12   1980s are particularly interesting (Ghio and Devlin, 2001; Dye et al., 2001; Wu et al., 2001;

13   Soukup et al., 2000; Frampton et al., 1999). Epidemiological studies by Pope et al. (1989, 1991)

14   and reported in the previous PM AQCD (U.S. Environmental Protection Agency, 1996a) showed

15   that closure of an open-hearth steel mill over the winter of 1987 was associated with reductions

16   in hospital admissions for respiratory diseases (see Chapter 8 for details of the epidemiology

17   studies). Ambient PM was collected near the steel mill during the winter of 1986 (before

18   closure), 1987 (during closure), and again in 1988 (after plant reopening). The glass hi-vol filters

19   were stored, folded PM-side inward, in plastic sleeves at room temperature and humidity (Dye et

20   al., 2001). A description of the in vivo studies follows; the in vitro studies are discussed in

21   Section 7.5.2.1.

22   Ghio and Devlin (2001) investigated the biologic effect of PM from the Utah Valley to

23   determine if the biological responses mirrored the epidemiological findings, with greater injury

24   occurring after exposure to an equal mass of particles from those years in which the mill was in

25   operation. Aqueous extracts of the filters collected prior to closure of the steel mill, during the

26   closure and after its reopening, were instilled through a bronchoscope into the lungs of

27   nonsmoking volunteers. Twenty-four hours later, the same subsegment was lavaged. Exposure

28   to aqueous extracts of PM collected before closure and after reopening of the steel mill provoked

29   a greater inflammatory response than PM extract acquired during the plant shutdown. These

30   results indicate that the pulmonary effects observed after experimental exposure of humans to the

1   Utah Valley PM can be correlated with health outcomes observed in epidemiologic studies of the

2   same material under normal exposure conditions.

3   Dye et al (2001) examined the relationship between Utah Valley ambient PM and

4   respiratory health effects. Sprague-Dawley rats were intratracheally instilled with equivalent

5   masses of aqueous extracts from filters originally collected during the winter before, during, and

6   after closure of the steel mill. Twenty-four hours after instillation, rats exposed to extracts of

7   particles collected when the plant was open developed significant pulmonary injury and

8   neutrophilic inflammation. Additionally, 50% of rats exposed to these extracts had increased

9   airway responsiveness to acetylcholine, compared to 17 and 25% of rats exposed to saline or the

10 extracts of particles collected when the plant was closed. By 96 hr, these effects were largely

11 resolved except for increases in lung lavage fluid neutrophils and lymphocytes in rats exposed to

12 PM extracts from prior to the plant closing. Analogous effects were observed with lung

13 histologic assessment. Extract analysis demonstrated that nearly 70% of the mass in all three

14 extracts appeared to be sodium-based salts derived from the glass filter matrix. Extracts of

15 particles collected when the plant was open contained more sulfate, cationic salts (i.e., calcium,

16 potassium, magnesium), and certain metals (i.e., copper, zinc, iron, lead, strontium, arsenic,

17 manganese, nickel). Although total metal content was ≈1% of the extracts by mass, the greater

18 quantity detected in the extracts of particles collected when the plant was open suggests that

19 metals may be important determinants of the observed pulmonary toxicity. The authors conclude

20 that the pulmonary effects induced in rats by exposure to aqueous extracts of local ambient PM

21 filters were in good accord with the epidemiologic reports of adverse respiratory health effects in

22 Utah Valley residents.

23   The fact that instillation of ambient PM collected from different geographical areas and

24 from a variety of emission sources consistently caused pulmonary inflammation and injury tends

25 to corroborate epidemiological studies that report increased PM-associated respiratory effects in

26 populations living in many different geographical areas and climates. However, high-dose

27 instillation studies may produce different effects on the lung than inhalation exposures done at

28 more relevant concentrations. This concern is somewhat diminished by the results of inhalation

29 studies of concentrated PM in healthy nonsmokers.

30   Ghio et al. (2000a) exposed 38 healthy volunteers exercising intermittently at moderate

31 levels of exertion for 2 h to either filtered air or particles concentrated from the air in Chapel

1   Hill, NC (23 to 311 μg/m^2). Analysis of cells and fluid obtained 18 h after exposure showed a

2   mild increase in neutrophils in the bronchial and alveolar fractions of bronchoalveolar lavage

3   (BAL) in subjects exposed to the highest quartile concentration of concentrated PM (mean of

4   206.7 μg/m^3). Lavage protein did not increase, and there were no other indicators of pulmonary

5   injury. No respiratory symptoms or decrements in pulmonary function were found after exposure

6   to CAPs.

7   The 38 human volunteers reported in Ghio (2000a) were also examined for changes in host

8   defense and immune parameters in BAL and blood (Harder et al., 2001). There were no changes

9   in the number of lymphocytes or macrophages, subcategories of lymphocytes (according to

10   surface marker analysis by flow cytometry), cytokines IL-6 and IL-8, or macrophage

11   phagocytosis. Similarly, there was no effect of concentrated ambient PM exposure on

12   lymphocyte subsets in blood. Thus, a mild inflammatory response to concentrated ambient PM

13   was not accompanied by an affect on immune defenses as determined by lymphocyte or

14   macrophage effects.

15   Other human inhalation studies with CAPs are limited by the small numbers of subjects

16   studied. Petrovic et al., 1999 exposed four healthy volunteers (aged 18 to 40) under resting

17   conditions to filtered air and 3 concentrations of concentrated ambient PM (23 to 124 μg/m^3) for

18   2 hours using a face mask. The exposure was followed by 30 minutes of exercise. No cellular

19   signs of inflammation were observed in induced sputum samples collected at 2 or 24 hours after

20   exposure. There was a trend toward an increase in nasal lavage neutrophils although no

21   statistical significance was presented. The only statistically significant change in pulmonary

22   function was a 6.4% decrease in thoracic gas volume after exposure to 124 μg/m^3 PM versus a

23   5.6% increase after air. A similar, small pilot study has been reported (Gong et al., 2000) in

24   which no changes in pulmonary function or symptoms were observed in four subjects aged 19 to

25   41 after a 2 hour exposure to air or mean concentrations of 148 to 246 μg/m^3 concentrated

26   ambient PM in Los Angeles, CA. Both of these laboratories are currently expanding on these

27   preliminary findings, but no data are available at this time.

28

29   **7.2.1.2 Diesel Particulate Matter**

30   Other controlled human exposures of ambient PM that may be relevant to this discussion

31   were the DPM studies previously examined in detail in separate assessment documents (U.S.

1   Environmental Protection Agency, 2000; Health Effects Institute, 1995). Briefly, the data from

2   work shift studies suggest that the principle noncancer human hazard from exposure to diesel

3   exhaust (DE) includes increased acute sensory and respiratory symptoms (e.g., cough, phlegm,

4   chest tightness, wheezing) that are more sensitive indicators of possible health risks from

5   exposure to diesel exhaust than pulmonary function decrements. Immunological changes also

6   have been demonstrated under short-term exposure scenarios to either diesel exhaust or DPM,

7   and the evidence indicates that these immunological effects are caused by both the non-

8   extractable carbon core and the adsorbed organic fraction of the diesel particle. While noncancer

9   effects from long-term exposure to DPM of several laboratory animal species include pulmonary

10   histopathology and chronic inflammation, noncancer effects in humans from long-term chronic

11   exposure to DPM are not evident. The mode of action of DPM is not completely understood but

12   the effects on the upper respiratory tract, observed in acute studies, suggest an irritant mechanism

13   while the effects on the lung, observed in chronic studies, indicate an underlying inflammatory

14   response. Currently available data suggest that the carbonaceous core of the diesel particle, or

15   metabolites of metal components of the particle, are possible causative agents for the noncancer

16   lung effects which are mediated, at least in part, by a progressive impairment of alveolar

17   macrophage function. The noncancer lung effects occur in response to DPM in several species

18   and occur in rats at doses lower than those inducing particle overload.

19   Diesel particulate matter, therefore, can be relevant to the urban environment, particularly

20   in urban micro-environments with heavy diesel engine traffic. The findings of controlled studies

21   on DPM are included here and in Section 7.4.3 (allergic hosts/immunology).

22   Pulmonary function and inflammatory markers (as assayed in induced sputum samples or

23   BAL) have been studied in human subjects exposed to either resuspended or freshly generated

24   and diluted DPM. In a controlled human study, Sandstrom and colleagues (Rudell et al., 1994)

25   exposed eight healthy subjects in an exposure chamber to diluted exhaust from a diesel engine

26   for 1 h with intermittent exercise. Dilution of the diesel exhaust was controlled to provide a

27   median NO_2 level of approximately 1.6 ppm. Median particle number was 4.3×10^6 /cm^3, and

28   median levels of NO and CO were 3.7 and 27 ppm, respectively (particle size and mass

29   concentration were not provided). There were no effects on spirometry or on airway closing

30   volume. Five of eight subjects experienced unpleasant smell, eye irritation, and nasal irritation

31   during exposure. BAL was performed 18 hours after exposure and was compared with a control

1 BAL performed 3 weeks prior to exposure. There was no control air exposure. Small yet
2 statistically significant reductions were seen in BAL mast cells, AM phagocytic function, and
3 lymphocyte CD4 to CD8+ cell ratios. A small increase in neutrophils was also observed. These
4 findings suggest that diesel exhaust may induce mild airway inflammation in the absence of
5 spirometric changes. Although this early study provided important information on the effect of
6 diesel exhaust exposure in humans, only one exposure level was used, the number of subjects
7 was low, and a limited range of endpoints was reported. A number of follow-up studies have
8 been done by the same and other investigators.

9 Rudell et al. (1996) later exposed 12 healthy volunteers to diesel exhaust for 1 h in an
10 exposure chamber. Light work on a bicycle ergometer was performed during exposure.
11 Random, double-blinded exposures included air, diesel exhaust, or diesel exhaust with particle
12 numbers reduced 46% by a particle trap. The engine used was a new Volvo model 1990, a six-
13 cylinder direct-injection turbocharged diesel with an intercooler, which was run at a steady speed
14 of 900 rpm during the exposures. Comparison of this study with others is difficult because
15 neither exhaust dilution ratios nor particle concentrations were reported. Carbon monoxide
16 concentrations of 27-30 ppm and NO of 2.6-2.7 ppm, however, suggested DPM concentrations
17 may have equaled several mg/m^3. The most prominent symptoms during exposure were
18 irritation of the eyes and nose accompanied by an unpleasant smell. Both airway resistance and
19 specific airway resistance increased significantly during the exposures. Despite the 46%
20 reduction in particle numbers by the trap, effects on symptoms and lung function were not
21 significantly attenuated.

22 A follow-up study on the usefulness of a particle trap confirmed the lack of effect of the
23 filter on diesel exhaust-induced symptoms (Rudell et al., 1999). In this study, 10 healthy
24 volunteers also underwent BAL 24 hours after exposure. Exposure to diesel exhaust produced
25 inflammatory changes in BAL as evidenced by increases in neutrophils and decreases in
26 macrophage phagocytic function in vitro. A 50% reduction in the particle number concentration
27 by the particle trap did not alter these cellular changes in BAL. Salvi et al. (1999) exposed
28 healthy human subjects to diluted diesel exhaust (DPM = 300 μg/m^3) for 1 h with intermittent
29 exercise. As reported in the studies by Rudell and Sandstrom, significant increases in neutrophils
30 and B lymphocytes, as well as histamine and fibronectin in airway lavage fluid, were not
31 accompanied by decrements in pulmonary function. Bronchial biopsies obtained 6 h after diesel

1   exhaust exposure showed a significant increase in neutrophils, mast cells, and CD4+ and CD8+

2   T lymphocytes, along with upregulation of the endothelial adhesion molecules ICAM-1 and

3   vascular cell adhesion molecule-1 (VCAM-1) and increases in the number of leukoxyte function-

4   associated antogen-1 (LFA-1+) in the bronchial tissue. Importantly, extra-pulmonary effects

5   were observed in these subjects. Significant increases in neutrophils and platelets were observed

6   in peripheral blood following exposure to diesel exhaust.

7   In a follow-up investigation of potential mechanisms underlying the DE-induced airway

8   leukocyte infiltration, Salvi et al. (2000) exposed healthy human volunteers to diluted DE on two

9   separate occasions for 1 h each, in an exposure chamber. Fiber-optic bronchoscopy was

10 performed 6 h after each exposure to obtain endobronchial biopsies and bronchial wash (BW)

11 cells. These workers observed that diesel exhaust (DE) exposure enhanced gene transcription of

12 interleukin-8 (IL-8) in the bronchial tissue and BW cells and increased growth-regulated

13 oncogene-α protein expression and IL-8 in the bronchial epithelium; there was also a trend

14 toward an increase in interleukin-5 (IL-5) mRNA gene transcripts in the bronchial tissue.

15   Nightingale et al. (2000) have reported inflammatory changes in healthy volunteers

16 exposed to 200 μg/m^3 resuspended DPM under resting conditions in a double-blinded study.

17 Small but statistically significant increases in neutrophils and myeloperoxidase (an index of

18 neutrophil activation) were observed in sputum samples induced 4 hours after exposure to DPM

19 in comparison to air. Exhaled carbon monoxide was measured as an index of oxidative stress

20 and was found to increase maximally at 1 hour after exposure. These biochemical and cellular

21 changes occurred in the absence of any decrements in pulmonary function, thus suggesting that

22 markers of inflammation are more sensitive than pulmonary function measurements.

23   Because of the considerable concern regarding the inhalation of ambient particles by

24 sensitive subpopulations, Sandstrom's laboratory also studied the effect of a 1 hour exposure to

25 300 μg/m^3 DPM on 14 atopic asthmatics with stable disease on inhaled corticosteroid treatment

26 (Nordenhall et al., 2001). At 6 hours after exposure, there was a significant increase in IL-6 in

27 induced sputum. At 24 hours after exposure, there was a significant increase in the nonspecific

28 airway responsiveness to inhaled methacholine. Although the exposure level was high relative to

29 ambient PM levels, these findings are important in terms of their relation to the epidemiology

30 evidence of an increase in asthma morbidity associated with episodic exposure to ambient PM.

1   The role of antioxidant defenses in protecting against acute diesel exhaust exposure has

2   been studied. Blomberg et al. (1998) investigated changes in the antioxidant defense network

3   within the respiratory tract lining fluids of human subjects following diesel exhaust exposure.

4   Fifteen healthy, nonsmoking, asymptomatic subjects were exposed to filtered air or diesel

5   exhaust (DPM 300 mg/m^3) for 1 h on two separate occasions at least 3 weeks apart. Nasal lavage

6   fluid and blood samples were collected prior to, immediately after, and 5.5 h post-exposure.

7   Bronchoscopy was performed 6 h after the end of diesel exhaust exposure. Nasal lavage ascorbic

8   acid concentration increased tenfold during diesel exhaust exposure, but returned to basal levels

9   5.5 h post-exposure. Diesel exhaust had no significant effects on nasal lavage uric acid or GSH

10   concentrations and did not affect plasma, bronchial wash, or bronchoalveolar lavage antioxidant

11   concentrations or malondialdehyde or protein carbonyl concentrations. The authors concluded

12   that the acute increase in ascorbic acid in the nasal cavity induced by diesel exhaust may prevent

13   further oxidant stress in the respiratory tract of healthy individuals.

14

15   **7.2.1.3 Complex Combustion-Related Particles**

16   Because emission sources contribute to the overall ambient air particulate burden (Spengler

17   and Thurston, 1983), many of the studies investigating the response of laboratory animals to

18   particle exposures have used complex combustion-related particles for exposure (see Table 7-3).

19   For example, the residual oil fly ash (ROFA) samples used in toxicological studies have been

20   collected from a variety of sources such as boilers, bag houses used to control emissions from

21   power plants, and from the particles that are emitted downstream of the collection devices (see

22   Table 1).

23   ROFA has a high content of water soluble sulfate and metals, accounting for 82 to 92% of

24   water-soluble mass, while the water-soluble mass fraction in ambient air varies from low teens to

25   more than 60% (Costa and Dreher, 1997; Prahalad et al., 1999). More than 90% of the metals in

26   ROFA are transition metals; whereas these metals are only a small subfraction of the total

27   ambient PM mass. Thus, the dose of bioavailable metal that is delivered to the lung when ROFA

28   is instilled into a laboratory animal can be orders of magnitude greater than an ambient PM dose,

29   even under a worst-case scenario.

30   Intratracheal instillation of various doses of ROFA suspension has been shown to produce

31   severe inflammation, an indicator of pulmonary injury that includes recruitment of neutrophils,

1   eosinophils, and monocytes into the airway. The biological effects of ROFA in rats have been

2   shown to depend on aqueous leachable chemical constituents of the particles (Dreher et al., 1997;

3   Kodavanti et al., 1997b). A leachate prepared from ROFA, containing predominantly Fe, Ni, V,

4   Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA

5   suspension (Dreher et al., 1997). Depletion of Fe, Ni, and V from the ROFA leachate eliminated

6   its pulmonary toxicity. Correspondingly, minimal lung injury was observed in animals exposed

7   to saline-washed ROFA particles. A surrogate transition metal sulfate solution containing Fe, V,

8   and Ni largely reproduced the lung injury induced by ROFA. Interestingly, ferric sulfate and

9   vanadium sulfate antagonized the pulmonary toxicity of nickel sulfate. Interactions between

10   different metals and the acidity of PM were found to influence the severity and kinetics of lung

11   injury induced by ROFA and its soluble transition metals.

12   To further investigate the response to ROFA with differing metal and sulfate composition,

13   male Sprague-Dawley rats (60 days old) were exposed to ROFA or metal sulfates (iron,

14   vanadium, and nickel, individually or in combination) (Kodavanti et al., 1997b). Transition

15   metal sulfate mixtures caused less injury than ROFA or Ni alone, suggesting metal interactions.

16   In addition, this study showed that V-induced effects were less severe than that of Ni and were

17   transient. Ferric sulfate was least pathogenic. Cytokine gene expression was induced prior to the

18   pathology changes in the lung, and the kinetics of gene expression suggested persistent injury by

19   nickel sulfate. Another study by the same investigators was performed using 10 different ROFA

20   samples collected at various sites within a power plant burning residual oil (Kodavanti et al.,

21   1998a). Animals received intratracheal instillations of either saline (control), or a saline

22   suspension of whole ROFA (<3.0 μm MMAD) at three concentrations (0.833, 3.33, or

23   8.33 mg/kg). This study showed that ROFA-induced PMN influx was associated with its water-

24   leachable V content; however, protein leakage was associated with water-leachable Ni content.

25   ROFA-induced in vitro activation of alveolar macrophages (AMs) was highest with ROFA

26   containing leachable V but not with Ni plus V, suggesting that the potency and the mechanism of

27   pulmonary injury may differ between emissions containing bioavailable V and Ni.

28   Other studies have shown that soluble metal components play an important role in the

29   toxicity of emission source particles. Gavett et al. (1997) investigated the effects of two ROFA

30   samples of equivalent diameters, but having different metal and sulfate content, on pulmonary

31   responses in Sprague-Dawley rats. ROFA sample 1 (R1) (the same emission particles used by

1   Dreher et al. [1997]) had approximately twice as much saline-leachable sulfate, nickel, and

2   vanadium, and 40 times as much iron as ROFA sample 2 (R2); whereas R2 had a 31-fold higher

3   zinc content. Rats were instilled with suspensions of 2.5 mg R2 in 0.3 mL saline, the supernatant

4   of R2 (R2s), the supernatant of 2.5 mg R1 (R1s), or saline only. By 4 days after instillation, 4 of

5   24 rats treated with R2s or R2 had died. None of those treated with R1s or saline died.

6   Pathological indices, such as alveolitis, early fibrotic changes, and perivascular edema, were

7   greater in both R2 groups. In surviving rats, baseline pulmonary function parameters and airway

8   hyperreactivity to acetylcholine were significantly worse in the R2 and R2s groups than in the

9   R1s groups. Other than BAL neutrophils, which were significantly higher in the R2 and R2s

10   groups, no other inflammatory cells (macrophages, eosinophils, or lymphocytes) or biochemical

11   parameters of lung injury were significantly different between the R2 and R2s groups and the

12   R1s group. Although soluble forms of zinc had been found in guinea pigs to produce a greater

13   pulmonary response than other sulfated metals (Amdur et al., 1978), and, although the level of

14   zinc was 30-fold greater in R2 than R1, the precise mechanisms by which zinc may induce such

15   responses are unknown. Nevertheless, these results show that the composition of soluble metals

16   and sulfate is critical in the development of airway hyperractivity and lung injury produced by

17   ROFA, albeit at high concentrations.

18   Reactive oxygen species may play an important role in the in vivo toxicity of ROFA. Dye

19   et al. (1997) pretreated rats with an intraperitoneal injection of saline or dimethylthiourea

20   (DMTU) (500 mg/kg), followed 30 min later by intratracheal instillation of either acidic saline

21   (pH = 3.3) or an acidified suspension of ROFA (500 μg/rat). The systemic administration of

22   DMTU impeded development of the cellular inflammatory response to ROFA but did not

23   ameliorate biochemical alterations in BAL fluid. In a subsequent study, these investigators

24   determined that oxidant generation, possibly induced by soluble vanadium compounds in ROFA,

25   is responsible for the subsequent rat tracheal epithelial cells gene expression, inflammatory

26   cytokine production (MIP-2 and IL-6), and cytotoxicity (Dye et al., 1999).

27   In addition to transition metals, other components in fly ash also may cause lung injury.

28   The effects of arsenic compounds in coal fly ash or copper smelter dust on the lung integrity and

29   on the ex vivo release of TNFα by alveolar phagocytes were investigated by Broeckaert et al.

30   (1997). Female Naval Medical Research Institute (NMRI) mice were instilled with different

31   particles normalized for the arsenic content (20 μg/kg body weight [i.e., 600 ng arsenic/mouse])

1   and the particle load (100 mg/kg body weight [i.e., 3 mg/mouse]). Mice received tungsten

2   carbide (WC) alone, coal fly ash (CFA) alone, copper smelter dust (CMP) mixed with WC, and

3   $Ca_3(AsO_4)_2$ mixed with WC (see Table 7-2 for concentration details). Copper smelter dust

4   caused a severe but transient inflammatory reaction; whereas a persisting alveolitis (30 days

5   postexposure) was observed after treatment with coal fly ash. In addition, TNFα production in

6   response to lipopolysaccharide (LPS) by alveolar phagocytes were significantly inhibited at Day

7   1 but was still observed at 30 days after administration of CMP and CFA. Although arsenic was

8   cleared from the lung tissue 6 days after $Ca_3(AsO_4)_2$ administration, a significant fraction

9   persisted (10 to 15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at

10 Day 30. It is possible that suppression of TNF-α production is dependent upon the slow

11 elimination of the particles and their metal content from the lung.

12   In summary, intratracheally instilled ROFA produced acute lung injury and inflammation.

13 The water soluble metals in ROFA appear to play a key role in the acute effects of instilled

14 ROFA. Although studies done with ROFA clearly show that combustion generated particles

15 with a high metal content can cause substantial lung injury, there are still insufficient data to

16 extrapolate the high dose effects to the low levels of particle associated transition metals in

17 ambient PM.

18

19 **7.2.2 Acid Aerosols**

20   There have been extensive studies of the effects of controlled exposures to aqueous acid

21 aerosols on various aspects of lung function in humans and laboratory animals. Many of these

22 studies were reviewed in the previous criteria document (U.S. Environmental Protection Agency

23 1996a) and in the Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989);

24 some of the more recent studies are summarized in this document (Table 7-5). Methodology and

25 measurement methods for controlled human exposure studies have been reviewed elsewhere

26 (Folinsbee et al., 1997).

27   The studies summarized in the previous document illustrate that aqueous acidic aerosols

28 have minimal effects on symptoms and mechanical lung function in young healthy adult

29 volunteers at concentrations as high as 1000 $\mu g/m^3$. However, at concentrations as low as

30 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. Brief exposures (≤ 1 h) to low

31 concentrations (≈ 100 $\mu g/m^3$) may accelerate clearance while longer (multihour) exposures to

TABLE 7-5. RESPIRATORY EFFECTS OF ACID AEROSOLS IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effects of Particles	Reference
Dogs, beagle, healthy; n = 16	Neutral sulfite aerosol	Inhalation	1.5 mg/m³	1.0 μm MMAD σg = 2.2	16.5 h/day for 13 mo	Long-term exposure to particle-associated sulfur and hydrogen ions at concentrations close to ambient levels caused only subtle respiratory responses and no change in lung pathology.	Heyder et al. (1999)
	Acidic sulfate aerosol	Inhalation	5.7 mg/m³	1.1 μm MMAD σg = 2.0	6 h/day for 13 mo		
Humans, asthmatic; 13 M, 11 F	H_2SO_4 aerosol NH_4^+/SO_4^{-2} aerosol	Inhalation by face mask	500 μg/m³	9 μm MMAD 7 μm MMAD	1 h	Exposure to simulated natural acid fog did not induce bronchoconstriction nor change bronchial responsiveness in asthmatics.	Leduc et al. (1995)
Rats, female, Fischer 344; Guinea Pigs, female, Hartley	H_2SO_4 aerosol	Inhalation	94 mg/m³ 43 mg/m³	0.80 ± 1.89 σg 0.93 ± 2.11 σg	4h	Acid aerosol increased surfactant film compressibility in guinea pigs.	Lee et al. (1999)
Humans, healthy nonsmokers; 10 M, 2 F; 21-37 years old	H_2SO_4 aerosol	Inhalation	1,000 μg/m³	0.8-0.9 μm MMAD	3 h	No inflammatory responses; LDH activity in BAL was elevated. Effect on bacterial killing by macrophages was inconclusive; latex particle phagocytosis was reduced 28%.	Zelikoff et al. (1997)

H_2SO_4 = Sulfuric acid
BAL = Bronchoalveolar lavage
LDH = Lactate dehydrogenase
MMAD = Mass median aerodynamic diameter
MMD = Mass median diameter
σg = Geometric standard deviation

1   higher concentrations (>100 μg/m^3) can depress clearance. Asthmatic subjects appear to be more

2   100 μg/m^3, acid aerosols can alter mucociliary clearance. Brief exposures ($\leq$1 h) to low

3   concentrations ($\approx$100 μg/m^3) may accelerate clearance while longer (multihour) exposures to

4   higher concentrations (>100 μg/m^3) can depress clearance. Asthmatic subjects appear to be more

5   sensitive to the effects of acidic aerosols on mechanical lung function. Responses have been

6   reported in adolescent asthmatics at concentrations as low as 68 μg/m^3, and modest

7   bronchoconstriction has been seen in adult asthmatics exposed to concentrations $\geq$400 μg/m^3, but

8   the available data are not consistent.

9   A previously described, acid aerosol exposure in humans (1000 μg/m^3 H_2SO_4) did not

10   result in airway inflammation (Frampton et al., 1992), and there was no evidence of altered

11   macrophage host defenses. A more recent study by Zelikoff et al. (1997) compared the responses

12   of rabbits and humans exposed to similar concentrations of H_2SO_4 aerosol. For both rabbits and

13   humans, there was no evidence of PMN infiltration into the lung and no change in BAL fluid

14   protein level, although there was an increase in LDH in rabbits but not in humans. Macrophages

15   showed less antimicrobial activity in rabbits; insufficient data were available for humans.

16   Macrophage phagocytic activity was slightly reduced in rabbits but not in humans. Superoxide

17   production by macrophages was somewhat depressed in both species. No respiratory effects of

18   long-term exposure to acid aerosol were found in dogs (Heyder et al., 1999). Thus, recent studies

19   have not provided any additional evidence to unequivocally demonstrate that relevant

20   concentrations of aqueous acid aerosols contribute to the acute cardiopulmonary effects of

21   ambient PM.

22

23   ## 7.2.3 Metal Particles, Fumes, and Smoke

24   Data from occupational and laboratory animal studies reviewed in the previous criteria

25   document (U. S. Environmental Protection Agency, 1996a) indicated that acute exposures to very

26   high levels (hundreds of μg/m^3 or more) or chronic exposures to lower levels (up to 15 μg/m^3) of

27   metallic particles could have an effect on the respiratory tract. Therefore, it was concluded on

28   the basis of data available at that time that the metals at typical concentrations present in the

29   ambient atmosphere (1 to 14 μg/m^3) were not likely to have a significant acute effect in healthy

30   individuals. The metals include arsenic, cadmium, copper, nickel, vanadium, iron, and zinc.

31   Other metals found at concentrations less than 0.5 μg/m^3 were not reviewed in the previous

1   criteria document. However, more recently published data from high-dose laboratory animal

2   studies added to the existing PM data base indicate that particle-associated metals are among the

3   potential causal components of PM.

4   Since completion of the previous criteria document, only limited controlled human

5   exposure studies have been performed with particles other than acid aerosols (see Table 7-6).

6   Controlled inhalation exposure studies to high concentrations of two different fume particles,

7   MgO and ZnO, demonstrate the differences in response based on particle metal composition

8   (Kuschner et al., 1997). Up to 6400 mg/m^3/min cumulative dose of MgO had no effect on lung

9   function (spirometry, DL_{CO}), symptoms of metal fume fever, or changes in inflammatory

10   mediators or cells recovered by BAL. However, lower concentrations of ZnO fume (165 to

11   1110 mg/m^3/min) induced a neutrophilic inflammatory response in the airways 20 h

12   postexposure. Lavage fluid PMNs, TNF-α, and IL-8 were increased by ZnO exposure. Although

13   the concentrations used in these exposure studies exceed ambient levels by more than 1000-fold,

14   the absence of a response to an almost 10-fold higher concentration of MgO compared with ZnO

15   indicates that metal composition, in addition to particle size (ultrafine/fine), is an important

16   determinant of the observed health responses to inhaled PM.

17   Several metals, including zinc, chromium, cobalt, copper, and vanadium, have been shown

18   to stimulate cytokine release in cultured human pulmonary cells. Boiler makers, exposed

19   occupationally to approximately 400 to 500 μg/m^3 of fuel oil ash, which contains high levels of

20   soluble metals, showed acute nasal inflammatory responses characterized by increased

21   myeloperoxidase (MPO) and IL-8 levels; these changes were associated with increased vanadium

22   levels in the upper airway (Woodin et al., 1998). Irsigler et al. (1999) reported that V_2O_5 can

23   induce asthma and bronchial hyperreactivity in exposed workers.

24   Autopsy data suggest that chronic exposure to urban air pollution leads to an increased

25   retention of metals in human tissues. A comparison of autopsy cases in Mexico City from the

26   1950s with the 1980s indicated substantially higher (5- to 20-fold) levels of Cd, Co, Cu, Ni, and

27   Pb in lung tissue from the 1980s (Fortoul et al., 1996). Similar studies have examined metal

28   content in human blood and lung tissue (Tsuchiyama et al., 1997; Osman et al., 1998) with

29   similar results.

30

TABLE 7-6. RESPIRATORY EFFECTS OF METAL PARTICLES, FUMES, AND SMOKE IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Mice, Swiss	EHC-93 soluble metal salts	Intratracheal instillation	1 mg in 0.1 ml	$0.8 \pm 0.4 \mu m$	3 days	Solution containing all metal salts (Al, Cu, Fe, Pb, Mg, Ni, Zn) or ZnCl alone increased BAL inflammatory cells and protein.	Adamson et al. (2000)
Rats, SD; 60 days old	VSO_4 $NiSO_4$	Inhalation	0.3 - 2.4 mg/m³	N/A	6h/day x 4 days	V did not induce any significant changes in BAL or HR; Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at > 1.2 mg/m³; possible synergistic effects were found.	Campen et al. (2001)
Humans, healthy nonsmokers; 12 M, 4 F; 18-35 years old	Colloidal iron oxide	Bronchial instillation	5 mg in 10 mL	$2.6 \mu m$	1, 2, and 4 days after instillation	L-ferritin increased after iron oxide particle exposure; transferrin was decreased. Both lactoferrin and transferrin receptors were increased.	Ghio et al. (1998a)
Humans, vanadium plant workers; 40 M; 19-60 years old	V_2O_5	Inhalation	<0.05-1.53 mg/m³	N/A	Variable	12/40 workers had bronchial hyperreactivity that persisted in some for up to 23 mo.	Irsigler et al. (1999)
Humans, healthy nonsmokers; 4 M, 2 F; 21-43 years old	MgO ZnO	Inhalation	5.8-230 mg/m³	$99\% < 1.8 \mu m$ $29\% < 0.1 \mu m$	15-45 min	No significant differences in BAL inflammatory cell concentrations, BAL interleukins (IL-1, IL-6, IL-8), tumor necrosis factor, pulmonary function, or peripheral blood neutrophils.	Kuschner et al. (1997)
Humans, healthy nonsmokers; 27 M, 7 F; 20-36 years old	Fe_2O_3	Intrapulmonary instillation	3×10^8 microspheres in 10 mL saline.	$2.6 \mu m$	N/A	Transient inflammation induced initially (neutrophils, protein, LDH, IL-8) was resolved by 4 days postinstillation.	Lay et al. (1998)
Rats, Fischer 344. (250 g)	Fe_2O_3	Intratracheal instillation	7.7×10^7 microspheres in 5 mL saline	$2.6 \mu m$	N/A	Transient inflammation at 1 day postinstillation.	Lay et al. (1998)
Humans, healthy nonsmokers; 8 M, 8 F; 18-34 years old	Fe_2O_3	Inhalation	12.7 mg/m³	$1.5 \mu m$ $\sigma g = 2.1$	30 min	No significant difference in $^{98m}T_c$-DTPA clearance half-times, $D_L CO$, or spirometry	Lay et al. (2001)
Mice, NMRI; Mouse peritoneal macrophage	MnO_2	Intratracheal instillation; in vitro	0.037, 0.12, 0.75, 2.5 mg/animal	surface area of 0.16, 0.5; 17, 62 m²/g	Sacrificed at 5 days	LDH, protein and cellular recruitment increased with increasing surface area; freshly ground particles had enhanced cytotoxicity.	Lison et al. (1997)

TABLE 7-6 (cont'd). RESPIRATORY EFFECTS OF METAL PARTICLES, FUMES, AND SMOKE IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, WISTAR Furth; 7-week-old, Mice, C57BL6 and DBA3NCR	CdO Fume	Nose-only Inhalation	1.04 mg/m^3 Rats dose = 18.72 μg Mouse dose = 4.59 μg	CMD = 0.008 μm σg = 1.1	1 × 3 h	Mice created more metallothionein than rats, which may be protective of tumor formation.	McKenna et al. (1998)
Rats, M, F344, 175-225 g	TiO$_2$	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 mg/m^3 for 2 h; Instillation at 500 μg for fine, 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	Inflammation produced by intratracheal inhalation (both severity and persistence) was less than that produced by instillation; ultrafine particles produced greater inflammatory response than fine particles for both dosing methods.	Osier and Oberdörster (1997)
Rats, M. F344, 175-225 g	TiO$_2$	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 mg/m^3 for 2 h; Instillation at 500 μg for fine, 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	MIP-2 increased in lavage cells but not in supernatant in those groups with increased PMN (more in instillation than in inhalation; more in ultrafine than in fine); TNF-α levels had no correlation with either particle size or dosing methods.	Osier et al. (1997)
Rats	NaVO$_3$ VOSO$_4$ V$_2$O$_5$	Intratracheal instillation	21 or 210 μg V/kg (NaVO$_3$, VOSO$_4$ soluble) 42 or 420 μg V/kg (V$_2$O$_s$) less soluble	N/A	1 h or 10 days following instillation	PMN influx was greatest following VOSO$_4$, lowest for V$_2$O$_5$; VOSO$_4$ induced inflammation persisted longest; MIP-2 and KC (CXC chemokines) were rapidly induced as early as 1 h postinstillation and persisted for 48 h; Soluble V induced greater chemokine mRNA expression than insoluble V; AMs have the highest expression level.	Pierce et al. (1996)
Humans, boilermakers (18 M), 26-61 years old, and utility worker controls (11 M), 30-55 years old	ROFA	Inhalation of fuel-oil ash	0.4-0.47 mg/m^3 0.1-0.13 mg/m^3	10 μm	6 weeks	Exposure to fuel-oil ash resulted in acute upper airway inflammation, possibly mediated by increased IL-8 and PMNs.	Woodin et al. (1998)

CdO = Cadmium oxide
Fe$_2$O$_3$ = Iron oxide
MgO = Magnesium oxide
MnO$_2$ = Manganese oxide
NaVO$_3$ =
TiO$_2$ = Titanium oxide
VOSO$_4$ = Vanadium sulfate
V$_2$O$_5$ = Vanadium oxide
ZnO = Zinc oxide

BAL = Bronchoalveolar lavage
CMD = Count median diameter
IL = Interleukin
LDH = Lactate dehydrogenase
MIP-2 = Macrophage inflammatory protein-2
mRNA = Messenger RNA (ribonucleic acid)
N/A = Data not available

1   Iron is the most abundant of the elements that are capable of catalyzing oxidant generation

2   and also is present in ambient urban particles. Lay et al. (1998) and Ghio et al. (1998a) tested the

3   hypothesis that the human respiratory tract will attempt to diminish the added, iron-generated

4   oxidative stress. They examined the cellular and biochemical response of human subjects,

5   instilled via the intrapulmonary route, with a combination of iron oxyhydroxides that introduced

6   an oxidative stress to the lungs. Saline alone and iron-containing particles suspended in saline

7   were instilled into separate lung segments of human subjects. Subjects underwent

8   bronchoalveolar lavage at 1 to 91 days after instillation of 2.6-μm diameter iron oxide

9   agglomerates. Lay and colleagues found iron-oxide-induced inflammatory responses in both the

10   alveolar fraction and the bronchial fraction of the lavage fluid at 1 day postinstillation. Lung

11   lavage 24 h after instillation revealed decreased transferrin concentrations and increased ferritin

12   and lactoferrin concentrations, consistent with a host-generated response to decrease the

13   availability of catalytically reactive iron (Ghio et al., 1998a). Normal iron homeostasis returned

14   within 4 days of the iron particle instillation. The same iron oxide preparation, which contained

15   a small amount of soluble iron, produced similar pulmonary inflammation in rats. In contrast,

16   instillation of rats with two iron oxide preparations that contained no soluble iron failed to

17   produce injury or inflammation, thus suggesting that soluble iron was responsible for the

18   observed intrapulmonary changes. Although the total dose of iron oxide delivered acutely to the

19   lung segments (approximately 5 mg or 2.1×10^8 particles) is considerably higher than would be

20   deposited in the lung at the concentrations of iron present in ambient urban air (generally less

21   than 1 μg/m^3), only a small amount of the iron instilled in human subjects was "active."

22   Therefore, it is still not clear how the amount of active iron in the PM extract compares with the

23   iron found in ambient air particles.

24   In a subsequent inhalation study, Lay et al. (2001) studied the effect of iron oxide particles

25   on lung epithelial cell permeability. Healthy, nonsmoking human subjects inhaled 12.7 mg/m^3

26   low- and high-solubility iron oxide particles (MMAD = 1.5 μm and σg = 2.1) for 30 minutes.

27   Neither pulmonary function nor alveolar epithelial permeability, as assessed by pulmonary

28   clearance of technetium-labeled DPTA, was changed at 0.5 or 24 hours after exposure to either

29   type of iron oxide particle. Because the exposure concentration was so high, the data suggest that

30   metals may play little role in the adverse effects of ambient, urban PM. Ghio et al. (2001) have

31   reported a case study, however, in which acute exposure to oil fly ash from a domestic oil-

1   burning stove produced diffuse alveolar damage, difficulty in breathing, and symptoms of angina.

2   While steroid treatment led to rapid improvement in symptoms and objective measurements, this

3   report suggests that the high metal content of oil fly ash can alter the epithelial cell barrier in the

4   alveolar region.

5

7.2.4 Ambient Bioaerosols

7   Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxins, and plant

8   and animal debris. Such biological aerosols can produce various health effects including

9   irritation, infection, hypersensitivity, and toxic response. Bioaerosols present in the ambient

10   environment have the potential to cause disease in humans under certain conditions. However, it

11   was concluded in the previous criteria document (U.S. Environmental Protection Agency, 1996a)

12   that bioaerosols, at the concentrations present in the ambient environment, would not contribute

13   to the observed effects of particulate matter on human mortality and morbidity reported in PM

14   epidemiological studies. Moreover, bioaerosols generally represent a rather small fraction of the

15   measured urban ambient PM mass and are typically present even at lower concentrations during

16   the winter months when notable ambient PM effects have been demonstrated. Bioaerosols tend

17   to be in the coarse fraction of PM, but some bioaerosols including nonagglomerated bacteria and

18   fragmented pollens, are found in the fine fraction.

19   More recent inhalation studies on ambient bioaerosols are summarized in Table 7-7.

20   In vitro studies on particle-associated endotoxin are discussed in Section 7.5.2.2. Endotoxin,

21   a cell wall component of gram negative bacteria, is ubiquitous in the environment. Although

22   there is strong evidence that inhaled endotoxin plays a major role in the toxic effects of

23   bioaerosols encountered in the work place (Vogelzang et al., 1998; Castellan et al., 1984, 1987),

24   it is not clear whether ambient concentrations of endotoxin are sufficient to produce toxic

25   pulmonary or systemic effects in healthy or sick individuals.

26   Michel et al. (1997) examined the dose-response relationship to inhaled lipopolysaccharide

27   (LPS: the purified derivative of endotoxin) in normal healthy volunteers exposed to 0, 0.5, 5, and

28   50 μg of LPS. Inhalation of 5 or 50 μg of LPS resulted in increased PMNs in blood and sputum

29   samples. At the higher concentration, a slight (3%) but not significant decrease in FEV_1 was

30   observed. Cormier et al. (1998) reported an approximate 10% decline in FEV_1 and an increase in

31   methacholine airway responsiveness after a 5-h exposure inside a swine containment building.

TABLE 7-7. RESPIRATORY EFFECTS OF AMBIENT BIOAEROSOLS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rats, Fischer 344, 8 weeks to 20 months old, N = 3/group	LPS (endotoxin)	Inhalation	70 EU	0.72 μm σg = 1.6	12 min	Significant interaction of LPS and O_3 on inflammatory responses in young rats. O_3 and UF-C interacted with "priming" by LPS to produce greater PMN response. LPS has a priming effect on lung inflammatory response to O_3 and UF-C.	Elder et al. (2000a,b)
	UF carbon		100 μg/m^3	25 nm σg = 1.6	6 h		
	ozone		1 ppm				
Humans, healthy; 5 M, 4 F, 24 to 50 years of age	LPS (endotoxin)	Inhalation	0.5 μg 5.0 μg 50 μg	1 - 4 μm MMAD	30 min	Significant decrease in PMN luminol-enhanced chemiluminescence with 0.5 μg LPS; increase in blood CRP and PMNs, and increase in sputum PMNs, monocytes, and MPO with 5.0 μg LPS; increase in temperature, blood PMNs, blood and urine CRP, sputum PMNs, monocytes, lymphocytes, TNFα, and ECP with 50 μg LPS.	Michel et al. (1997)
Humans, healthy; 32 M, 32 F, 16 to 50 years of age	Indoor pool water spray	Inhalation	N/A	0.1 - 7.5 μm	N/A	Recurring outbreaks of pool-associated granulomatous pneumonitis (n = 33); case patients had higher cumulative work hours. Analysis indicated increased levels of endotoxin in pool air and water.	Rose et al. (1998)
Humans, pig farmers, 82 symptomatic and 89 asymptomatic n = 171	Dust	Inhalation	2.63 mg/m^3 σg = 1.3	N/A	5 h/day average lifetime exposure	Large decline in FEV$_1$ (73 ml/year) and FVC (55 ml/year) associated with long-term average exposure to endotoxin.	Vogelzang et al. (1998)
	Endotoxin		105 ng/m^3 σg = 1.5				
Humans, potato plant workers, low exposures (37 M), high exposures (20 M)	Endotoxin	Inhalation	21.2 EU/m^3 low σg = 1.6 55.7 EU/m^3 high σg = 2.1	N/A	8 h	Decreased FEV$_1$, FVC, and MMEF over the work shift that was concentration related; endotoxin effects on lung function can be expected above 53 EU/m^3 ($\approx$4.5 ng/m^3) over 8 h.	Zock et al. (1998)

1   This exposure induced significant neutrophilic inflammation in both the nose and the lung.

2   Although these exposures are massive compared to endotoxin levels in ambient PM in U.S.

3   cities, these studies serve to illustrate the effects of endotoxin and associated bioaerosol material

4   in healthy nonsensitized individuals.

5   Some health effects have been observed after occupational exposure to complex aerosols

6   containing endotoxin at concentrations relevant to ambient levels. Zock et al. (1998) reported a

7   decline in FEV_1 (≈3%) across a shift in a potato processing plant with up to 56 endotoxin units

8    $(EU)/m^3$ in the air. Rose et al. (1998) reported a high incidence (65%) of BAL lymphocytes in

9   lifeguards working at a swimming pool where endotoxin levels in the air were on the order of

10   $28 EU/m^3$. Although these latter two studies may point towards pulmonary changes at low

11   concentrations of airborne endotoxin, it is not possible to rule out the contribution of other agents

12   in these complex organic aerosols. The contribution of endotoxin to the toxicity of ambient PM

13   has been studied in vitro, and these studies provide preliminary evidence that endotoxin

14   contamination of ambient PM may play a role in the observed in vitro effects (discussed in

15   Section 7.5).

16

17

18   **7.3 CARDIOVASCULAR AND SYSTEMIC EFFECTS OF PARTICULATE**
19   **   MATTER IN HUMANS AND LABORATORY ANIMALS: IN VIVO**
20   **   EXPOSURES**

21   A growing number of epidemiology studies have demonstrated that increases in cardiac-

22   related deaths are associated with exposure to PM (U.S. Environmental Protection Agency,

23   1996a) and that PM-related cardiac deaths appear to be as great or greater than those attributed to

24   respiratory causes (see Chapter 8). The toxicological consequences of inhaled particles on the

25   cardiovascular system had not been extensively investigated prior to 1996. Since then (see

26   Table 7-8), Costa and colleagues (e.g., Costa and Dreher, 1997) have demonstrated that

27   intratracheal instillation of high levels of ambient particles can increase or accelerate death in an

28   animal model of cardiorespiratory disease related to monocrotaline administration in rats. These

29   deaths did not occur with all types of ambient particles tested. Some dusts, such as volcanic ash

30   from Mount Saint Helens, were relatively inert; whereas other ambient dusts, including those

31   from urban sites, were toxic. These early observations suggested that particle composition plays

TABLE 7-8. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
Rats, male, F-344; 200-250 g	OTT	Nose-only Inhalation	40 mg/m³	4 to 5 μm MMAD	4 h	Increased plasma levels of endothelin-1. No acute lung injury; however, lung NO production decreased and macrophage inflammatory protein-2 from lung lavage cells increased after exposure.	Bouthillier et al. (1998)
Rats, male, S-D, 60 days old, MCT-treated and healthy, n = 64	ROFA	Instillation	0.0, 0.25, 1.0, and 2.5 mg/rat	1.95 μm	Analysis at 96 h	Dose-related hypothermia and bradycardia in healthy rats, potentiated by compromised models.	Campen et al. (2000)
Dogs, female mongrel, 14 to 17 kg	CAPs	Inhalation via tracheostomy	3-360 μg/m³	0.2 to 0.3 μm	6 h/day for 3 days	Peripheral blood parameters were related to specific particle constituents. Factor analysis from paired and crossover experiments showed that hematologic changes were not associated with increases in total CAP mass concentration.	Clarke et al. (2000a)
Rats, male, S-D, 60 days old, MCT-treated, and healthy	Emission source PM Ambient airshed PM ROFA	Instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 and 96 h following instillation	ROFA alone induced some mild arrhythumas; MCT-ROFA showed enhanced neutrophilic inflammation; MCT-ROFA animals showed more numerous and severe arrhythmias including S-T segment inversions and A-V block.	Costa and Dreher (1997)
Rats, male, S-D; 60 days old	ROFA	Instillation	0.3, 1.7, or 8.3 mg/kg	1.95 μm σg = 2.19	Analysis at 24 h	Increased plasma fibrinogen at 8.3 mg/kg only.	Gardner et al. (2000)
Humans, healthy nonsmokers, 18 to 40 years old	CAPs	Inhalation	23.1 to 311.1 μg/m³	0.65 μm σg = 2.35	2 h, analysis at 18 h	Increased blood fibrinogen.	Ghio et al. (2000a)
Dogs, mongrel, some with balloon occluded LAD coronary artery, n = 14	CAPs	Inhalation via tracheostomy	69-828 μg/m³	0.23 to 0.34 μm σg = 0.2 to 2.9	6 h/day for 3 days	Decreased time to ST segment elevation and increased magnitude in compromised dogs. Decreased heart and respiratory rate and increased lavage fluid neutrophils in normal dogs.	Godleski et al. (2000)
Rats	CAPs	Nose-only inhalation	110-350 μg/m³	N/A	3 h	Small but consistent increase in HR; no pulmonary injury was found; increased peripheral blood neutrophils and decreased lymphocytes.	Gordon et al. (1998)
Rats, male, F-344, MCT-treated Hamsters, 6-8 mo old; Bio TO-2	CAPs	Inhalation	132-919 μg/m³	0.2-1.2 μm σg = 0.2-3.9	3 h, evaluated at 3 and 24 h	No increase in cardiac arrhythmias; PM associated increases in HR and blood cell differential counts, and atrial conduction time of rats were inconsistent. No adverse cardiac or pulmonary effects in hamsters.	Gordon et al. (2000)
Rats, S-D, MCT-treated, 250 g	FOFA	Inhalation	580 ± 110 μg/m³	2.06 μm MMAD σg = 1.57	6 h/day for 3 days	Increased expression of the proinflammatory chemokine MP-2 in the lung and heart of MCT-treated rats; less in healthy rats. Significant mortality only in MCT-treated rats.	Killingsworth et al. (1997)

TABLE 7-8 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
Rats, male WKY and SH, 12 to 13-week-old	ROFA	Nose-only inhalation	15 mg/m³	N/A	6 h/day for 3 days	Cardiomyopathy and monocytic cell infiltration, along with increased cytokine expression, was found in left ventricle of SH rats because of underlying cardiovascular disease. ECG showed exacerbated ST segment depression caused by ROFA.	Kodavanti et al. (2000b)
Rats, male SH and WKY; 12-13 weeks old	ROFA from a precipitator of an oil-burning power plant	Inhalation; and acute intratracheal instillation	15 mg/m³ 1 and 5 mg/kg	1.5 μm σ_g = 1.5	6 h/days, 3 days per week for 1, 2, or 4 weeks	IT exposure increased plasma fibrinogen and decreased peripheral lymphocytes in both SH and WKY rats. Acute IH exposure increased plasma fibrinogen in SH rats only; longer exposure caused pulmonary injury but no changes in fibrinogen.	Kodavanti et al. (2002)
Dogs, beagles, 10.5-year- old, healthy, n = 4	ROFA	Oral inhalation	3 mg/m³	2.22 μm MMAD σg = 2.71	3 h/day for 3 days	No consistent changes in ST segment, the form or amplitude of the T wave, or arrhythmias; slight bradycardia during exposure.	Muggenburg et al. (2000)
Rabbits, female, New Zealand White, 1.8 to 2.4 kg	Colloidal carbon	Instillation	2 mL of 1% colloidal carbon (20 mg)	<1 μm	Examined for 24 to 192 h after instillation	Colloidal carbon stimulated the release of BRDU-labeled PMNs from the bone marrow. The supernatant of alveolar macrophages treated with colloidal carbon in vitro also stimulated the release of PMNs from bone marrow, likely via cytokines.	Terashima et al. (1997)
Rats, Wistar	Ottawa ambient (EHC-93) (ECH-93L) Diesel soot (DPM) Carbon black (CB)	Inhalation (nose only)	48 mg/m3 49 mg/m3 5 mg/m3 5mg/m3	36, 56, 80, 100, and 300 μm	4 h	EHC-93 elevated blood pressure and ET-1 and ET-3 levels EHC-93 L No effect on blood pressure, transient effect on ET-1, -2, -3 levels DPM no effect on blood pressure, but elevated ET-3 levels CB no effect	Vincent et al. (2001)
Rats, male, S-D, MCT-treated	ROFA	Instillation	0.25, 1.0, or 2.5 mg in 0.3 mL saline	1.95 μm MMAD σg = 2.19	Monitored for 96 h after instillation of ROFA particles	Dose-related increases in the incidence and duration of serious arrhythmic events in normal rats. Incidence and severity of arrythmias were increased greatly in the MCT rats. Deaths were seen at each instillation level in MCT rats only (6/12 died after MCT + ROFA).	Watkinson et al. (1998)

TABLE 7-8 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
(1) Rats, S-D healthy and cold-stressed, ozone-treated, and MCT-treated	ROFA	Intratracheal instillation	0.0, 0.25, 1.0, or 2.5 mg/rat	1.95 μm	Monitored for 96 h after instillation	(1) Healthy rats exposed IT to ROFA demonstrated dose-related hypothermia, bradycardia, and increased arrhythmias. Compromised rats demonstrated exaggerated hypothermia and cardiac responses to IT ROFA. Mortality was seen only in the MCT-treated rats exposed to ROFA by IT. (2) Pulmonary hypertensive (MCT-treated S-D) and systemically hypertensive (SH) rats exposed to ROFA by inhalation demonstrated similar effects, but of diminished amplitude. There were no lethalities by the inhalation route. (3) Older rats exposed IT to OTT showed a pronounced biphasic hypothermia and a severe drop in HR accompanied by increased arrhythmias; exposure to ROFA caused less pronounced, but similar effects. No cardiac effects were seen with exposure to MSH. (4) Ni and V showed the greatest toxicity; Fe-exposed rats did not differ from controls.	Watkinson et al. (2000a,b)
(2) Rats, S-D, SH rats, WKY rats, healthy and MCT-treated,	ROFA	Inhalation	15 mg/m^3	1.95 μm	6 h/day for 3 days		
(3) Rats, SH, 15-mo-old	OTT ROFA MSH	Intratracheal instillation	2.5 mg 0.5 mg 2.5 mg	1.95 μm	Monitored for 96 h after instillation		
(4) Rats, S-D MCT-treated	$Fe_2(SO_4)_3$ VSO_4 $NiSO_2$	Intratracheal instillation	105 μg 245 μg 262.5 μg	1.95 μm	Monitored for 96 h after instillation		

1   an important role in the adverse health effects associated with episodic exposure to ambient PM,

2   despite the "general particle" effect attributed to the epidemiological associations of ambient PM

3   exposure and increased mortality in many regions of the United States (i.e., regions with varying

4   particle composition). Work that examines the role of inherent susceptibility to the adverse

5   effects of PM in compromised animal models of human pathophysiology provides a potentially

6   important link to epidemiological observations and is discussed below.

7   To date, studies examining the systemic and cardiovascular effects of particles have used a

8   number of compromised animal models, largely rodent models. Two studies in normal or

9   compromised dogs (Godleski et al., 2000; Muggenburg et al., 2000) also have been published as

10   well as the preliminary results from studies in which human subjects were exposed to

11   concentrated ambient PM (see Section 7.4.1). Although the majority of animal studies

12   examining the systemic effects of PM have used metal-laden ROFA as a source particle, a

13   growing number of studies have used collected and stored ambient PM or real-time generated

14   concentrated ambient particles. The following discussion of the systemic effects of PM first

15   describes the ROFA studies and then compares these findings with the ambient PM studies.

16   Killingsworth and colleagues (1997) used a fuel oil fly ash to examine the adverse effects

17   of a model urban particle in an animal model (monocrotaline, MCT) of cardiorespiratory disease;

18   MCT causes progressive lung injury and vascular inflammation in rats. The lung injury induced

19   with MCT can lead, within two weeks of treatment, to pulmonary hypertension and right heart

20   enlargement, common features of chronic obstructive pulmonary disease in humans. They

21   observed 42% mortality in MCT rats exposed to approximately 580 $\mu g/m^3$ fly ash for 6 h/day for

22   3 consecutive days. Deaths did not occur in MCT rats exposed to filtered air or in saline-treated

23   rats exposed to fly ash. The increase in deaths in the MCT/fly ash group was accompanied by an

24   increase in neutrophils in lavage fluid and an increased immunostaining of MIP-2 in the heart

25   and lungs of the MCT/fly ash animals. Cardiac immunohistochemical analysis indicated

26   increased MIP-2 in cardiac macrophages. The fly ash-induced deaths did not result from a

27   change in pulmonary arterial pressure and the cause of death was not identified.

28   In a similar experimental model, Watkinson et al. (1998) examined the effects of

29   intratracheally instilled ROFA (0.0, 0.25, 1.0, 2.5 mg in 3 mL saline) on ECG measurements in

30   control and MCT rats. They observed a dose-related increase in the incidence and duration of

31   serious arrhythmic events in control animals exposed to ROFA particles, and these effects were

1   clearly exacerbated in the MCT animals. Similar to the results of Killingsworth et al. (1997),

2   healthy animals treated with ROFA suffered no deaths, but there were 1, 2, and 3 deaths in the

3   low-, medium-, and high-dose MCT groups, respectively. Thus, ROFA PM was linked to the

4   conductive and hypoxemic arrhythmias associated with cardiac-related deaths in the MCT

5   animals.

6   To examine the biological relevance of intratracheal instillation of ROFA particles,

7   Kodavanti et al. (1999) exposed MCT rats to ROFA by either instillation (0.83 or 3.33 mg/kg) or

8   nose-only inhalation (15 mg/m^3, 6 h/day for 3 consecutive days). Similar to Watkinson et al.

9   (1998), intratracheal instillation of ROFA in MCT rats resulted in ≈50% mortality. Notably, no

10   mortality occurred in MCT rats exposed to ROFA by the inhalation route despite the high

11   exposure concentration (15 mg/m^3). In addition, no mortality occurred in healthy rats exposed to

12   ROFA or in MCT rats exposed to clean air. Despite the fact that mortality was not associated

13   with ROFA inhalation exposure of MCT rats, exacerbation of lung lesions and pulmonary

14   inflammatory cytokine gene expression, as well as ECG abnormalities, clearly were evident.

15   Watkinson and colleagues further examined the effect of instilled ROFA in rodents

16   previously exposed to ozone or housed in the cold (Watkinson et al., 2000a,b; Campen et al.,

17   2000). The effect of ozone-induced pulmonary inflammation (preexposure to 1 ppm ozone for

18   6 h) or housing in the cold (10 °C) on the response to instilled ROFA in rats was similar to that

19   produced with MCT. Bradycardia, arrhythmias, and hypothermic changes were consistently

20   observed in the ozone exposed and hypothermic animals treated with ROFA, although, unlike in

21   the MCT animals, no deaths occurred. Thus, in rodents with cardiopulmonary disease/stress,

22   instillation of 0.25 mg or more of ROFA can produce systemic changes that may be used to study

23   potential mechanisms of toxicity that are consistent with the epidemiology and panel studies

24   showing cardiopulmonary effects in humans.

25   While studies of instilled residual oil fly ash demonstrated immediate and delayed

26   responses, consisting of bradycardia, hypothermia, and arrhythmogenesis in conscious,

27   unrestrained rats (Watkinson et al., 1998; Campen et al., 2000), further study of instilled ROFA-

28   associated transition metals showed that vanadium induced the immediate responses, while

29   nickel was responsible for the delayed effects (Campen et al., 2002a). Moreover, Ni, when

30   administered concomitantly, potentiated the immediate effects caused by V.

1   In another study, Campen et al. (2001) examined the responses to these metals in conscious
2   rats by whole-body inhalation exposure. The authors attempted to ensure valid dosimetric
3   comparisons with the instillation studies, by using concentrations of V and Ni ranging from 0.3-
4   2.4 mg/m^3. The concentrations used in this study incorporated estimates of total inhalation dose
5   derived using different ventilatory parameters. Heart rate (HR), core temperature (T[CO]), and
6   electrocardiographic (ECG) data were measured continuously throughout the exposure. Animals
7   were exposed to aerosolized Ni, V, or Ni + V for 6 h per day for 4 days, after which serum and
8   bronchoalveolar lavage samples were taken. While Ni caused delayed bradycardia, hypothermia,
9   and arrhythmogenesis at concentrations > 1.2 mg/m^3, V failed to induce any significant change in
10   HR or T (CO), even at the highest concentration. When combined, Ni and V produced
11   observable delayed effects at 0.5 mg/m^3 and potentiated responses at 1.3 mg/m^3, greater than
12   were produced by the highest concentration of Ni (2.1 mg/m^3) alone. Although these studies
13   were performed at metal concentrations that were orders of magnitude greater than ambient
14   concentrations, the results indicate a possible synergistic relationship between inhaled Ni and V.
15   Watkinson and colleagues (2000a,b) also sought to examine the relative toxicity of
16   different particles on the cardiovascular system of spontaneously hypertensive rats. They
17   instilled 2.5 mg of representative particles from ambient (Ottawa) or natural (Mount Saint Helens
18   volcanic ash) sources and compared the response to 0.5 mg ROFA. Instilled particles were either
19   mass equivalent dose or adjusted to produce equivalent metal dose. They observed adverse
20   changes in ECG, heart rate, and arrhythmia incidence that were much greater in the Ottawa- and
21   ROFA-treated rats than in the Mount Saint Helens-treated rats. The cardiovascular changes
22   observed with the Ottawa particles were actually greater than with the ROFA particles. These
23   series of experiments by Watkinson and colleagues clearly demonstrate that instillation of
24   ambient air particles, albeit at a very high concentration, can produce cardiovascular effects.
25   They also demonstrate that PM exposures of equal mass dose did not produce the same
26   cardiovascular effects, suggesting that PM composition was responsible for the observed effects.
27   Because of concerns regarding the relevance of particles administered by intratracheal
28   instillation, investigators also have examined the cardiovascular effects of ROFA particles using
29   more realistic inhalation exposure protocols. Kodavanti et al. (2000b) found that exposure to a
30   high concentration of ROFA (15 mg/m^3 for 6 h/day for 3 days) produced alterations in the ECG
31   waveform of spontaneously hypertensive (SH) but not normotensive rats. Although the ST

1   segment area of the ECG was depressed in the SH rats exposed to air, further depressions in the

2   ST segment were observed at the end of the 6-h exposure to ROFA on Days 1 and 2. The

3   enhanced ST segment depression was not observed on the third day of exposure, suggesting that

4   adaptation to the response had occurred. Thus, exposure to a very high concentration of ROFA

5   exacerbated a defect in the electroconductivity pattern of the heart in an animal model of

6   hypertension. This ROFA-induced alteration in the ECG waveform was not accompanied by an

7   enhancement in the monocytic cell infiltration and cardiomyopathy that also develop in SH rats.

8   Further work is necessary to determine the relevance of this ROFA study to PM at concentrations

9   relevant to ambient exposures.

10   Godleski and colleagues (2000) have performed a series of experiments examining the

11 cardiopulmonary effects of inhaled concentrated ambient PM on normal mongrel dogs and on

12 dogs with coronary artery occlusion. Dogs were exposed by inhalation via a tracheostomy tube

13 to concentrated ambient PM for 6 h/day for 3 consecutive days. The investigators found little

14 biologically-relevant evidence of pulmonary inflammation or injury in normal dogs exposed to

15 PM (daily range of mean concentrations was approximately 100 to 1000 $\mu g/m^3$). The only

16 statistically significant effect observed was a doubling of the percentage of neutrophils in lung

17 lavage. Despite the absence of major pulmonary effects, a significant increase in heart rate

18 variability (an index of cardiac autonomic activity), a decrease in heart rate, and an increase in T

19 alternans (an index of vulnerability to ventricular fibrillation) were observed. Exposure

20 assessment of particle composition produced no specific components of the particles that were

21 correlated with the day-to-day variability in response. The significance of these effects is not yet

22 clear because the effects did not occur on all exposure days. For example, the change in heart

23 rate variability was observed on only 10 of the 23 exposure days. Although the heart rate

24 variability change and the increase in T alternans suggest a possible proarrhythmic response to

25 inhaled concentrated ambient PM, the clinical significance of this effect is currently unknown.

26   The most important finding in the experiments of Godleski et al. (2000) was the

27 observation of a potential increase in ischemic stress of the cardiac tissue from repeated exposure

28 to concentrated ambient PM. During coronary occlusion in four dogs exposed to PM, they

29 observed a significantly more rapid development of ST elevation of the ECG waveform.

30 In addition, the peak ST-segment elevation was greater after PM exposure. Together, these

31 changes suggest that concentrated ambient PM can augment the ischemia associated with

1   coronary artery occlusion in this dog model. Additional work in more dogs as well as other

2   species is necessary to determine the significance of these findings to the human response to

3   ambient PM.

4   Muggenburg and colleagues (2000) reported that inhalation exposure to high

5   concentrations of ROFA produces no consistent changes in amplitude of the ST-segment, form

6   of the T wave, or arrhythmias in dogs. In their studies, four beagle dogs were exposed to

7   3 mg/m^3 ROFA particles for 3 h/day for 3 consecutive days. They noted a slight but variable

8   decrease in heart rate, but the changes were not statistically or biologically significant. The

9   transition metal content of the ROFA used by Muggenburg was approximately 15% by mass,

10   a value that is on the order of a magnitude higher than that found in ambient urban PM samples.

11   Although the study did not specifically address the effect of metals, it suggests that inhalation of

12   high concentrations of metals may have little effect on the cardiovascular system of a healthy

13   individual.

14   In a series of studies, Gordon, Nadziejko, and colleagues examined the response of the

15   rodent cardiovascular system to concentrated ambient PM derived from New York City air

16   (Gordon et al., 2000). Particles of 0.2 to 2.5 μm in diameter were concentrated up to 10 times

17   their levels in ambient air ($\approx$150 to 900 μg/m^3) to maximize possible differences in effects

18   between normal and cardiopulmonary-compromised laboratory animals. ECG changes were not

19   detected in normal Fischer 344 rats or hamsters exposed by inhalation to concentrated ambient

20   PM for 1 to 3 days. Similarly, no deaths or ECG changes were observed in MCT rats or

21   cardiomyopathic hamsters exposed to PM. Contrary to the decrease in heart rate observed in

22   dogs exposed to concentrated ambient PM (Godleski et al., 2000), heart rate was increased in

23   both normal and MCT rats exposed to PM. The increase was approximately 5% and was not

24   observed on all exposure days. Thus, extrapolation of the heart rate changes in these animal

25   studies to human health effects is difficult, although the increase in heart rate in rats is similar to

26   that observed in some human population studies.

27   Gordon and colleagues (1998) have reported other cardiovascular effects in animals

28   exposed to inhaled CAP. Increases in peripheral blood platelets and neutrophils were observed

29   in control and MCT rats at 3 h, but not 24 h, after exposure to 150 to 400 μg/m^3 concentrated

30   ambient PM (CAP). This neutrophil effect did not appear to be dose related and did not occur on

31   all exposure days, suggesting that day-to-day changes in particle composition may play an

1   important role in the systemic effects of inhaled particles. The number of studies reported was

2   small and; therefore, it is not possible to statistically determine if the day-to-day variability was

3   truly due to differences in particle composition or even to determine the size of this effect.

4   Terashima et al. (1997) also examined the effect of particles on circulating neutrophils. They

5   instilled rabbits with 20 mg colloidal carbon, a relatively inert particle (<1 μm), and observed a

6   stimulation of the release of 5'-bromo-2'deoxyuridine (BrdU)-labeled PMNs from the bone

7   marrow at 2 to 3 days after instillation. Because the instilled supernatant from rabbit AMs

8   treated in vitro with colloidal carbon also stimulated the release of PMNs from the bone marrow,

9   the authors hypothesized that cytokines released from activated macrophages could be

10 responsible for this systemic effect. The same research group (Tan et al., 2000) looked for

11 increased white blood cell counts as a marker for bone marrow PMN precursor release in humans

12 exposed to high levels of carbon from biomass burning during the 1997 Southeast Asian smoke-

13 haze episodes. They found a significant association between PM_{10} (1-day lag) and elevated band

14 neutrophil counts expressed as a percentage of total PMNs. The biological relevance of this

15 latter study to urban PM-induced systemic effects in unclear, however, because of the high dose

16 of carbon particles.

17   The results of epidemiology studies have suggested that homeostatic changes in the

18 vascular system can occur after episodic exposure to ambient PM. Studies by Vincent et al.

19 (2001) indicate that urban particles inhaled by laboratory rats can affect blood levels of

20 endothelin and cause a vasopressor response without causing acute lung injury. Moreover, the

21 potency to influence hemodynamic changes can be modified by removing the polar organic

22 compounds and soluble elements from the particles. In the study described previously

23 (Section 7.2.3), Ghio et al. (2000a) also have shown that inhalation of concentrated PM in

24 healthy nonsmokers causes increased levels of blood fibrinogen. They exposed 38 volunteers

25 exercising intermittently at moderate levels of exertion for 2 h to either filtered air or particles

26 concentrated from the air in Chapel Hill, NC (23 to 311 μg/m^2). Blood obtained 18 h after

27 exposure contained significantly more fibrinogen than blood obtained before exposure. The

28 observed effects in blood may be associated with the mild pulmonary inflammation also found

29 18 h after exposure to CAP (see Section 7.2.3).

30   Gardner et al. (2000) examined whether the instillation of particles would alter blood

31 coagulability factors in laboratory animals. Sprague-Dawley rats were instilled with 0.3, 1.7, or

1   8.3 mg/kg of ROFA or 8.3 mg/kg Mount Saint Helens volcanic ash. They observed an increase

2   in plasma fibrinogen in healthy rats. Because fibrinogen is a known risk factor for ischemic heart

3   disease and stroke, the authors suggested that this alteration in the coagulation pathway could

4   take part in the triggering of cardiovascular events in susceptible individuals. Elevations in

5   plasma fibrinogen, however, were observed in healthy rats only at the highest treatment dose; and

6   no other changes in clotting function were noted. Because the lower treatment doses are known

7   to cause pulmonary injury and inflammation, albeit to a lower extent, the absence of plasma

8   fibrinogen changes at these lower doses suggests that only high levels of pulmonary injury are

9   able to produce an effect in healthy test animals.

10   To establish the temporal relationship between pulmonary injury, increased plasma

11   fibrinogen, and changes in peripheral lymphocytes, Kodavanti et al., (2002) exposed

12   Spontaneously Hypertensive (SH) and Wistar-Kyoto (WKY) rats to ROFA using both

13   intratracheal and inhalation exposure (acute and long-term) scenarios. Increases in plasma

14   fibrinogen and decreases in circulating white blood cells were found during the acute phase

15   responses to ROFA exposure and were temporally associated with acute, but not long-term, lung

16   injury. A bolus intratracheal instillation of ROFA increased plasma fibrinogen in both SH and

17   WKY rats; whereas the increase was evident only in SH rats after acute ROFA inhalation. The

18   increased fibrinogen in SH rats corresponded to an inability to find increased pulmonary

19   glutathione and greater pulmonary injury and inflammation than was found in the WKY rats.

20   In summary, controlled animal studies have provided initial evidence that only high

21   concentrations of inhaled or instilled particles can have systemic, especially cardiovascular,

22   effects. In the case of MCT rats, these effects can be lethal. Controlled human exposure studies

23   also have shown ambient levels of inhaled PM can produce some biochemical and cellular

24   changes in the blood. Although some of these biochemical changes have been used as clinical

25   "markers" for cardiovascular diseases, the causal relationship between these changes and the

26   potential life-threatening diseases remains to be established. Understanding the pathways by

27   which very small concentrations of inhaled ambient PM can produce systemic, life-threatening

28   changes also is far from clear. Among the hypotheses that have been proposed to account for the

29   nonpulmonary effects of PM are activation of neural reflexes, cytokine effects on heart tissue

30   (Killingsworth et al., 1997), alterations in coagulability (Seaton et al., 1995; Sjögren, 1997),

31   perturbations in both conductive and hypoxemic arrythmogenic mechanisms (Watkinson et al.,

1998; Campen et al., 2000), and altered endothelin levels (Vincent et al., 2001). A great deal of research using controlled exposures of laboratory animals and human subjects to PM will be necessary to test mechanistic hypotheses generated to date, as well as those that are likely to be proposed in the future (see Section 7.5).

7.4 SUSCEPTIBILITY TO THE EFFECTS OF PARTICULATE MATTER EXPOSURE

Susceptibility of an individual to adverse health effects of PM can vary depending on a variety of host factors such as age, physiological activity profile, genetic predisposition, or preexistent disease. The potential for preexistent disease to alter adverse response to toxicant exposure is widely acknowledged but poorly understood. Because of inherent variability (necessitating large numbers of subjects) and ethical concerns associated with using diseased subjects in clinical research studies, a solid database on human susceptibilities is lacking. For more control over both host and environmental variables, animal models often are used. However, care must be taken in extrapolation from animal models of human disease to humans. Rodent models of human disease, their use in toxicology, and the criteria for judging their appropriateness as well as their limitations must be considered (Kodavanti et al., 1998b; Kodavanti and Costa, 1999).

7.4.1 Pulmonary Effects of Particulate Matter in Compromised Hosts

Epidemiological studies suggest there may be subsegments of the population that are especially susceptible to effects from inhaled particles (see Chapter 8). The elderly with chronic cardiopulmonary disease, those with pneumonia and possibly other lung infections, and those with asthma (at any age) appear to be at higher risk than healthy people of similar age. Unfortunately, most toxicology studies have used healthy adult animals. An increasing number of newer studies have examined effects of ambient particles in compromised host models. Costa and Dreher (1997) used a rat model of cardiopulmonary disease to explore the question of susceptibility and the possible mechanisms by which PM effects are potentiated. Rats with advanced monocrotaline (MCT)-induced pulmonary vasculitis/hypertension were given intratracheal instillations of ROFA (0, 0.25, 1.0, and 2.5 mg/rat). The MCT animals had a

marked neutrophilic inflammation. In the context of this inflammation, ROFA induced a four- to fivefold increase in BAL PMNs. There was increased mortality at 96 h that was ROFA-dose dependent. The results of this study indicate that particles, albeit at a high concentration, enhanced mortality in MCT animals but not in healthy animals.

As discussed previously, Kodavanti et al. (1999) also studied PM effects in the MCT rat model of pulmonary disease. Rats treated with 60 mg/kg MCT were exposed to 0, 0.83. or 3.3 mg/kg ROFA by intratracheal instillation and to 15 mg/m^3 ROFA by inhalation. Both methods of exposure caused inflammatory lung responses; and ROFA exacerbated the lung lesions, as shown by increased lung edema, inflammatory cells, and alveolar thickening.

The manner in which MCT can alter the response of rats to inhaled particles was examined by Madl and colleagues (1998). Rats were exposed to fluorescent colored microspheres (1 μm) 2 weeks after treatment with MCT. In vivo phagocytosis of the microspheres was altered in the MCT rats in comparison with control animals. Fewer microspheres were phagocytized in vivo by alveolar macrophages, and there was a concomitant increase in free microspheres overlaying the epithelium at airway bifurcations. The decrease in in vivo phagocytosis was not accompanied by a similar decrease in vitro. Macrophage chemotaxis, however, was impaired significantly in MCT rats compared with control rats. Thus, MCT appeared to impair particle clearance from the lungs via inhibition of macrophage chemotaxis.

The sulfur dioxide (SO$_2$)-induced model of chronic bronchitis has also been used to examine the potential interaction of PM with preexisting lung injury. Clarke and colleagues pretreated Sprague-Dawley rats for 6 weeks with air or 170 ppm SO$_2$ for 5 h/day and 5 days/week (Clarke et al., 1999). Exposure to concentrated ambient air particles for 5 h/day for 3 days at an average concentration of 515 μg/m^3 produced significant changes in both cellular and biochemical markers in lavage fluid. In comparison to control animal values, protein was increased approximately threefold in SO$_2$-pretreated animals exposed to concentrated ambient PM. Lavage fluid neutrophils and lymphocytes were increased significantly in both groups of rats exposed to concentrated ambient PM, with greater increases in both cell types in the SO$_2$-pretreated rats. Thus, exposure to concentrated ambient PM produced adverse changes in the respiratory system, but no deaths, in both normal rats and in a rat model of chronic bronchitis.

Clarke et al. (2000b) next examined the effect of concentrated ambient PM from Boston, MA, in normal rats of different ages. Unlike the earlier study that used Sprague-Dawley rats,

1 4- and 20-mo-old Fischer 344 rats were examined after exposure to concentrated ambient PM for

2 5 h/day for 3 consecutive days. They found that exposure to the daily mean concentrations of 80,

3 170, and 50 μg/m^3 PM, respectively, produced statistically significant increases in total

4 neutrophil counts (over 10-fold) in lavage fluid of the young, but not the old, rats. Thus, repeated

5 exposure to relatively low concentrations of ambient PM produced an inflammatory response,

6 although the actual percent neutrophils in the concentrated ambient PM-exposed young adult rats

7 was low (approximately 3%). On the other hand, Gordon et al. (2000) found no evidence of

8 neutrophil influx in the lungs of normal and monocrotaline-treated Fischer 344 rats exposed in

9 nine separate experiments to concentrated ambient PM from New York, NY, as high as

10 400 μg/m^3 for a 6-h exposure or 192 μg/m^3 for three daily 6-h exposures. Similarly, normal and

11 cardiomyopathic hamsters showed no evidence of pulmonary inflammation or injury after a

12 single exposure to the same levels of concentrated ambient PM. Gordon and colleagues did

13 report a statistically significant doubling in protein concentration in lavage fluid in

14 monocrotaline-treated rats exposed for 6 h to 400 μg/m^3 concentrated ambient PM. Because of

15 the disparity in findings in the response of normal Fischer 344 rats to concentrated ambient PM

16 between these two labs, it is important that the reproducibility of these experiments be examined.

17   Kodavanti and colleagues (1998b) also have examined the effect of concentrated ambient

18 PM in normal rats and rats with sulfur dioxide-induced chronic bronchitis. Among the four

19 separate exposures to PM, there was a significant increase in lavage fluid protein in bronchitic

20 rats from only one exposure protocol in which the rats were exposed to 444 and 843 μg/m^3 PM

21 on 2 consecutive days (6 h/day). Neutrophil counts were increased in bronchitic rats exposed to

22 concentrated ambient PM in three of the four exposure protocols, but was decreased in the fourth

23 protocol. No other changes in normal or bronchitic rats were observed, even in the exposure

24 protocols with higher PM concentrations. Thus, rodent studies have demonstrated that

25 inflammatory changes can be produced in normal and compromised animals exposed to

26 concentrated ambient PM. These findings are important because only a limited number of

27 studies have used real-time inhalation exposures to actual ambient urban PM.

28   Pulmonary function measurements are often less invasive than other means to assess the

29 effects of inhaled air pollutants on the mammalian lung. After publication of the 1996 PM

30 AQCD, a number of investigators examined the response of rodents and dogs to inhaled ambient

31 particles. In general, these investigators have demonstrated that ambient PM has minimal effects

1   on pulmonary function tests. Gordon et al. (2000) exposed normal and monocrotaline-treated

2   rats to filtered air or 181 μg/m^3 concentrated ambient PM for 3 h. For both normal and

3   monocrotaline-treated rats, no differences in lung volumes or diffusion capacities for carbon

4   monoxide were observed between the air or PM exposed animals at 3 or 24 h after exposure.

5   Similarly, in cardiomyopathic hamsters, concentrated ambient PM had no effect on these same

6   pulmonary function measurements.

7   Other pulmonary function endpoints have been studied in animals exposed to concentrated

8   ambient PM. Clarke et al. (1999) observed that tidal volume was increased slightly in both

9   control rats and rats with sulfur dioxide-induced chronic bronchitis exposed to 206 to 733 μg/m^3

10   PM on 3 consecutive days. No changes in peak expiratory flow, respiratory frequency, or minute

11   volume were observed after exposure to concentrated ambient PM. In the series of dog studies

12   by Godleski et al. (2000) (also see Section 7.3), no signficant changes in pulmonary function

13   were observed in normal mongrel dogs exposed to concentrated ambient PM, although a 20%

14   decrease in respiratory frequency was observed in dogs that underwent coronary artery occlusion

15   and were exposed to PM. Thus, studies using normal and compromised animal models exposed

16   to concentrated ambient PM have found minimal biological effects of ambient PM on pulmonary

17   function.

18   Johnston et al. (1998) exposed 8-week-old mice (young) and 18-mo-old mice (old) to

19   polytetrafluoroethylene (PTFE) fumes (0, 10, 25, and 50 μg/m^3) for 30 min. Lung lavage

20   endpoints (PMN, protein, LDH, and β-glucuronidase) as well as lung tissue mRNA levels for

21   various cytokines, metallothionein and for Mn superoxide dismutase were measured 6 h

22   following exposure. Protein, lymphocyte, PMN, and TNF-α mRNA levels were increased in

23   older mice when compared to younger mice. These findings suggest that the inflammatory

24   response to PTFE fumes is altered with age, being greater in the older animals. Although

25   ultrafine PTFE fumes are not a valid surrogate for ambient ultrafine particles (Oberdörster et al.,

26   1992), this study did provide evidence to support the hypothesis that particle-induced pulmonary

27   inflammation is different between young and old mice. Further studies on age-related PM effects

28   are described in Section 7.6 (Responses to PM and Gaseous Pollutant Mixtures).

29   Kodavanti et al. (2000b; 2001) used genetically predisposed spontaneously hypertensive

30   (SH) rats as a model of cardiovascular disease to study PM-related susceptibility. The SH rats

31   were found to be more susceptible to acute pulmonary injury from intratracheal ROFA exposure

1	than normotensive control Wistar Kyoto (WKY) rats (Kodavanti et al., 2001). The primary

2	metal constituents of ROFA, V and Ni, caused differential species-specific effects. Vanadium,

3	which was less toxic than Ni in both strains, caused inflammatory responses only in WKY rats;

4	whereas Ni was injurious to both WKY and SH rats (SH > WKY). This differential

5	responsiveness of V and Ni was correlated with their specificity for airway and parenchymal

6	injury, discussed in another study (Kodavanti et al., 1998b). When exposed to the same ROFA

7	by inhalation, SH rats were more sensitive than WKY rats in regards to vascular leakage

8	(Kodavanti et al., 2000b). The SH rats exhibited a hemorrhagic response to ROFA. Oxidative

9	stress was much higher in ROFA exposed SH rats than matching WKY rats. Also, SH rats,

10	unlike WKY rats, showed a compromised ability to increase BALF glutathione in response to

11	ROFA, suggesting a potential link to increased susceptibility. Cardiovascular effects were

12	characterized by ST-segment area depression of the ECG in ROFA-exposed SH but not WKY

13	rats. When the same rats were exposed to ROFA by inhalation (Kodavanti et al., 2002),

14	differences in effects were found depending on the length of exposure. After acute exposure,

15	increased plasma fibrinogen was associated with lung injury; longer-term, episodic ROFA

16	exposure resulted in progressive protein leakage and inflammation that was significantly worse in

17	SH rats when compared to WKY rats. These studies demonstrate the potential utility of

18	cardiovascular disease models for the study of PM health effects and show that genetic

19	predisposition to oxidative stress and cardiovascular disease may play a role in sensitivity to

20	increased PM-related cardiopulmonary injury.

21	 On the basis of in vitro studies, Sun et al. (2001) predicted that the antioxidant and lipid

22	levels in the lung lining fluid may determine susceptibility to inhaled PM. In a subsequent study

23	from the same laboratory, Norwood et al. (2001) conducted inhalation studies on guinea pigs to

24	test this hypothesis. The guinea pigs were divided on the basis of dietary supplementation or

25	depletion of ascorbic acid (C) and glutathione (GSH) into four groups: (+C+GSH), (+C-GSH),

26	(-C+GSH), and (-C-GSH). All groups were exposed, nose-only, to clean air or 19-25 mg/m^3

27	ROFA ($<$ 2.5 µm) for 2 h. Nasal lavage and BAL fluid and cells were examined at 0 h and 24 h

28	postexposure. Exposure to ROFA increased lung injury in the (-C-GSH) group only, as shown

29	by increased BAL fluid protein, LDH, and PMNs and decreased BAL macrophages, and resulted

30	in lower antioxidant concentrations in BAL fluid than were found with single deficiencies.

1   In summary, although more of these studies are just emerging and are only now being

2   replicated or followed more thoroughly to investigate the mechanisms, they do provide evidence

3   of enhanced susceptibility to inhaled PM in "compromised" hosts.

4

7.4.2 Genetic Susceptibility to Inhaled Particles and their Constituents

6   A key question in understanding the adverse health effects of inhaled PM is which

7   individuals are susceptible to PM. Although factors such as age and health status have been

8   studied in both epidemiology and toxicology studies, a number of investigators have begun to

9   examine the importance of genetic susceptibility in the response to inhaled particles because of

10   considerable evidence that genetic factors play a role in the response to inhaled pollutant gases.

11   To accomplish this goal, investigators typically have studied the interstrain response to particles

12   in rodents. The response to ROFA instillation in different strains of rats has been investigated by

13   Kodavanti et al. (1996, 1997a). In the first study, male Sprague-Dawley (SD) and Fischer-344

14   (F-344) rats were instilled intratracheally with saline or ROFA particles. ROFA instillation

15   produced an increase in lavage fluid neutrophils in both SD and F-344 rats; whereas a time-

16   dependent increase in eosinophils occurred only in SD rats. In the subsequent study (Kodavanti

17   et al., 1997a), SD, Wistar (WIS), and F-344 rats (60 days old) were exposed to saline or ROFA

18   (8.3 mg/kg) by intratracheal instillation and examined for up to 12 weeks. Histology indicated

19   focal areas of lung damage showing inflammatory cell infiltration as well as alveolar, airway, and

20   interstitial thickening in all three rat strains during the week following exposure. Trichrome

21   staining for fibrotic changes indicated a sporadic incidence of focal alveolar fibrosis at 1, 3, and

22   12 weeks in SD rats; whereas WIS and F-344 rats showed only a modest increase in trichrome

23   staining in the septal areas. One of the isoforms of fibronectin mRNA was upregulated in

24   ROFA-exposed SD and WIS rats, but not in F-344 rats. Thus, in rats there appears to be a

25   genetic based difference in susceptibility to lung injury induced by instilled ROFA.

26   Differences in the degree of pulmonary inflammation have been described in rodent strains

27   exposed to airborne pollutants. To understand the underlying causes, signs of airway

28   inflammation (i.e., airway hyper-responsiveness, inflammatory cell influx) were established in

29   responsive (BABL/c) and non-responsive (C57BL/6) mouse strains exposed to ROFA (Veronesi

30   et al., 2000). Neurons taken from the ganglia (i.e., dorsal root ganglia) that innervate the nasal

31   and upper airways were cultured from each mouse strain and exposed to ROFA. The difference

1   in inflammatory response noted in these mouse strains *in vivo* was retained in culture, with

2   C57BL/6 neurons showing significantly lower signs of biological activation (i.e., increased

3   intracellular calcium levels) and cytokine (i.e., IL-6, IL-8) release relative to BALB/c mice.

4   RT-PCR and immunocytochemistry indicated that the BALB/c mouse strain had a significantly

5   higher number of neuropeptide and acid-sensitive (i.e., NK1, VR1) sensory receptors on their

6   sensory ganglia relative to the C57BL/6 mice. Such data indicate that genetically-determined

7   differences in sensory inflammatory receptors can influence the degree of PM-induced airway

8   inflammation.

9   Kleeberger and colleagues have examined the role that genetic susceptibility plays in the

10   effect of inhaled acid-coated particles on macrophage function. Nine inbred strains of mice were

11   exposed nose-only to carbon particles coated with acid (10 mg/m^3 carbon with 285 μg/m^3 sulfate)

12   for 4 h (Ohtsuka et al., 2000a). Significant inter-strain differences in Fc-receptor-mediated

13   macrophage phagocytosis were observed, with C57BL/6J mice being the most sensitive.

14   Although neutrophil counts were increased more in C3H/HeOuJ and C3H/HeJ strains of mice

15   than in the other strains, the overall magnitude of change was small and not correlated with the

16   changes in macrophage phagocytosis. In follow-up studies using the same type particle, Ohtsuka

17   et al. (2000a,b) performed a genome-wide scan with an intercross cohort derived from C57BL/6J

18   and C3H/HeJ mice. Analyses of macrophage dysfunction phenotypes of segregant and

19   nonsegregant populations derived from these two strains indicate that two unlinked genes control

20   susceptibility. They identified a 3-centiMorgan segment on mouse chromosome 17 that contains

21   an acid-coated particle susceptibility locus. Interestingly, this quantitative trait locus overlaps

22   with those described for ozone-induced inflammation (Kleeberger et al., 1997) and acute lung

23   injury (Prows et al., 1997) and contains several promising candidate genes that may be

24   responsible for the observed genetic susceptibility for macrophage dysfunction in mice exposed

25   to acid-coated particles.

26   Leikauf and colleagues (Leikauf et al., 2000; Wesselkamper et al., 2000; McDowell et al.,

27   2000; Prows and Leikauf, 2001; Leikauf et al., 2001) have identified a genetic susceptibility in

28   mice that is associated with mortality following exposures to high concentrations (from 15 to 150

29   μg/m^3) of a NiSO4 aerosol (0.22 μm MMAD) for up to 96 h. These studies also have

30   preliminarily identified the chromosomal locations of a small number of genes that may be

31   responsible for this genetic susceptibility. This finding is particularly significant in light of the

1   toxicology studies demonstrating that bioavailable, first-row transition metals participate in the

2   acute lung injury following exposure to emission and ambient air particles. Similar genes may be

3   involved in human responses to particle-associated metals. However, additional studies will be

4   required to determine whether the identified metal susceptibility genes are involved in human

5   responses to ambient levels of particulate-associated metals.

6   One study has examined the interstrain susceptibility to ambient particles. C57BL/6J and

7   C3H/HeJ mice were exposed to 250 μg/m^3 concentrated ambient PM$_{2.5}$ for 6 h and examined at

8   0 and 24 h after exposure for changes in lavage fluid parameters and cytokine mRNA expression

9   in lung tissue (Shukla et al., 2000). No interstrain differences in response were observed.

10   Surprisingly, although no indices of pulmonary inflammation or injury were increased over

11   control values in the lavage fluid, increases in cytokine mRNA expression were observed in both

12   murine strains exposed to PM$_{2.5}$. Although the increase in cytokine mRNA expression was

13   generally small (approximately twofold), the effects on IL-6, TNF-α, TGF-β2, and γ-interferon

14   were consistent.

15   Thus, a handful of studies have begun to demonstrate that genetic susceptibility can play a

16   role in the response to inhaled particles. However, the doses of PM administered in these

17   studies, whether by inhalation or instillation, were extremely high when compared to ambient

18   PM levels. Similar strain differences in response to inhaled metal particles have been observed

19   by other investigators (McKenna et al., 1998; Wesselkamper et al., 2000), although the

20   concentration of metals used in these studies were also more relevant to occupational rather than

21   environmental exposure levels. It remains to be determined whether genetic susceptibility plays

22   as significant a role in the adverse effects of ambient PM as does age or health status.

23

24   7.4.3 Effect of Particulate Matter on Allergic Hosts

25   Relatively little is known about the effects of inhaled particles on humoral (antibody) or

26   cell-mediated immunity. Alterations in the response to a specific antigenic challenge have been

27   observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 μg/m^3)

28   (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported

29   an enhanced response to nonspecific bronchoprovocation agents, such as acetylcholine and

30   histamine, after exposure to inhaled particles. This nonspecific airway hyperresponsiveness,

31   a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under

1   controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although, its

2   relevance to specific allergic responses in the airways of atopic individuals is unclear, it

3   demonstrates that the airways of asthmatics may become sensitized to either specific or

4   nonspecific triggers that could result in increases in asthma severity and asthma-related hospital

5   admissions (Peters et al., 1997; Jacobs et al., 1997; Lipsett et al., 1997). Combustion particles

6   also may serve as carrier particles for allergens (Knox et al., 1997).

7   A number of in vivo and in vitro studies have demonstrated that DPM can alter the immune

8   response to challenge with specific antigens and suggest that DPM may act as an adjuvant.

9   These studies have shown that treatment with DPM enhances the secretion of antigen-specific

10   IgE in mice (Takano et al., 1997) and in the nasal cavity of human subjects (Diaz-Sanchez et al.,

11   1996, 1997; Ohtoshi et al., 1998). Because IgE levels play a major role in allergic asthma

12   (Wheatley and Platts-Mills, 1996), upregulation of its production could lead to an increased

13   response to inhaled antigen in particle-exposed individuals.

14   Van Zijverden et al. (2000a,b) used mouse models to assess the potency of particles to

15   adjuvate an immune response to a protein antigen. All particles exert an adjuvant effect on the

16   immune response to co-administered antigen, apparently stimulated by the particle core rather

17   than the attached chemical factors. Different particles, however, stimulate distinct types of

18   immune responses. In one model (Van Zijverden et al., 2001), BALB/c mice were intranasally

19   treated with a mixture of antigen (model antigen TNP-Ovalbumin, TNP-OVA) and particles on

20   three consecutive days. On day 10 after sensitization mice were challenged with the antigen

21   TNP-OVA alone and five days later the immune response was assessed. DPM, as well as carbon

22   black particles (CB), were capable of adjuvating the immune response to TNP-OVA as

23   evidenced by an increase of TNP-specific antibody (IgG1 and IgE) secreting B cells antibodies in

24   the lung-draining lymph nodes. Increased antigen-specific IgG1, IgG2a, and IgE isotypes were

25   measured in the serum, indicating that the response resulted in systemic sensitization.

26   Importantly, an increase of eosinophils in the bronchio-alveolar lavage was observed with CB.

27   Companion studies with the intranasal exposure model showed that the adjuvant effect of

28   particles (CB) was even more pronounced when the particles were given during both the

29   sensitization and challenge phases; whereas administration during the challenge phase caused

30   only marginal changes on the immune response. These data show that particulate matter can

31   increase both the sensitization and challenge responses to a protein antigen, and the immune

1   stimulating activity of particles appears to be a time-dependent process, suggesting that an

2   inflammatory microenvironment, such as may be created by the particles, is crucial for enhancing

3   sensitization by particles.

4   Only a small number of studies have examined the mechanisms underlying the

5   enhancement of allergic asthma by ambient urban particles. Ohtoshi et al. (1998) reported that a

6   coarse size-fraction of resuspended ambient PM, collected in Tokyo, induced the production of

7   granulocyte macrophage colony stimulating factor (GMCSF), an upregulator of dendritic cell

8   maturation and lymphocyte function, in human airway epithelial cells in vitro. In addition to

9   increased GMCSF, epithelial cell supernatants contained increased IL-8 levels when incubated

10   with DPM, a principal component of ambient particles collected in Tokyo. Although the sizes of

11   the two types of particles used in this study were not comparable, the results suggest that ambient

12   PM, or at least the DPM component of ambient PM, may be able to upregulate the immune

13   response to inhaled antigen through GMCSF production. Similarly, Takano et al. (1998) has

14   reported airway inflammation, airway hyperresponsiveness, and increased GMGSF and IL-5 in

15   mice exposed to diesel exhaust.

16   In a study by Walters et al. (2001), PM_{10} was found to induce airway hyperresponsiveness,

17   suggesting that PM exposure may be an important factor in increases in asthma prevalence.

18   Naive mice were exposed to a single dose (0.5 mg/ mouse) of ambient PM, coal fly ash, or diesel

19   PM. Exposure to PM_{10} induced increases in airway responsiveness and BAL cellularity; whereas

20   diesel PM induced significant increases in BAL cellularity, but not airway responsiveness.

21   On the other hand, coal fly ash exposure did not elicit significant changes in either of these

22   parameters. Ambient PM-induced airway hyperresponsiveness was sustained over 7 days. The

23   increase in airway responsiveness was preceded by increases in BAL eosinophils; whereas a

24   decline in airway responsiveness was associated with increases in macrophages. Thus, ambient

25   PM can induce asthma-like parameters in naive mice.

26   In an examination of the effect of concentrated ambient PM on airway responsiveness in

27   mice, Goldsmith and colleagues (1999) exposed control and ovalbumin-sensitized mice to an

28   average concentration of 787 μg/m^3 PM for 6 h/day for 3 days. Although ovalbumin

29   sensitization itself produced an increase in the nonspecific airway responsiveness to inhaled

30   methylcholine, concentrated ambient PM did not change the response to methylcholine in

31   ovalbumin-sensitized or control mice. For comparison, these investigators examined the effect

1   of inhalation of an aerosol of the active soluble fraction of ROFA on control and ovalbumin-

2   sensitized mice and demonstrated that ROFA could produce nonspecific airway

3   hyperresponsiveness to methylcholine in both control and ovalbumin-sensitized mice. Similar

4   increases in airway responsiveness have been observed after exposure to ROFA in normal and

5   ovalbumin-sensitized rodents (Gavett et al., 1997, 1999; Hamada et al., 1999, 2000).

6   Gavett et al. (1999) have investigated the effects of ROFA (intratracheal instillation) in

7   ovalbumin (OVA) sensitized and challenged mice. Instillation of 3 mg/kg (approximately 60 μg)

8   ROFA induced inflammatory and physiological responses in the OVA mice that were related to

9   increases in Th2 cytokines (IL-4, IL-5). Compared to OVA sensitization alone, ROFA induced

10   greater than additive increases in eosinophil numbers and in airway responsiveness to

11   methylcholine.

12   Hamada et al. (1999, 2000) have examined the effect of a ROFA leachate aerosol in a

13   neonatal mouse model of allergic asthma. In the first study, neonatal mice sensitized by

14   intraperitoneal (ip) injection with OVA developed airway hyperresponsiveness, eosinophilia, and

15   elevated serum anti-ovalbumin IgE after a challenge with inhaled OVA. Exposure to the ROFA

16   leachate aerosol had no marked effect on the airway responsiveness to inhaled methacholine in

17   nonsensitized mice, but did enhance the airway hyperresponsiveness to methylcholine produced

18   in OVA-sensitized mice. No other interactive effects of ROFA exposure with OVA were

19   observed. In a subsequent study, Hamada et al. clearly demonstrated that, whereas inhaled OVA

20   alone was not sufficient to sensitize mice to a subsequent inhaled OVA challenge, pretreatment

21   with a ROFA leachate aerosol prior to the initial exposure to aerosolized OVA resulted in an

22   allergic response to the inhaled OVA challenge. Thus, exposure to a ROFA leachate aerosol can

23   alter the immune response to inhaled OVA both at the sensitization stage at an early age and at

24   the challenge stage.

25   Lambert et al. (1999) also examined the effect of ROFA on a rodent model of pulmonary

26   allergy. Rats were instilled intratracheally with 200 or 1,000 μg ROFA 3 days prior to

27   sensitization with house dust mite (HDM) antigen. HDM sensitization after 1000 μg ROFA

28   produced increased eosinophils, LDH, BAL protein, and IL-10 relative to HDM alone. The

29   immediate bronchoconstrictive and associated antigen-specific IgE response to a subsequent

30   antigen challenge was increased in the ROFA-treated group in comparison with the control

31   group. Together, these studies suggest the components of ROFA can augment the immune

1 response to antigen. Evidence that metals are responsible for the ROFA-enhancement of an

2 allergic sensitization was demonstrated by Lambert et al. (2000). In this follow-up study, Brown

3 Norway rats were instilled with 1 mg ROFA or the three main metal components of ROFA (iron,

4 vanadium, or nickel) prior to sensitization with instilled house dust mite. The three individual

5 metals were found to augment different aspects of the immune response to house dust mite.

6 Nickel and vanadium produced an enhanced immune response to the antigen as seen by higher

7 house dust mite-specific IgE serum levels after an antigen challenge at 14 days after sensitization.

8 Nickel and vanadium also produced an increase in the lymphocyte proliferative response to

9 antigen in vitro. In addition, the antigen-induced bronchoconstrictive response was greater only

10 in nickel-treated rats. Thus, instillation of metals at concentrations equivalent to those present in

11 the ROFA leachate mimicked the response to ROFA, suggesting that the metal components of

12 ROFA are responsible for the increased allergic sensitization observed in ROFA-treated animals.

13   Although these studies demonstrate that inhalation or instillation of ROFA augments the

14 immune response in allergic hosts, the applicability of these findings to ambient PM is an

15 important consideration. Goldsmith et al. (1999) have compared the effect of inhalation of

16 concentrated ambient PM for 6 h/day for 3 days versus the effect of a single exposure to a ROFA

17 leachate aerosol on the airway responsiveness to methylcholine in OVA-sensitized mice.

18 Exposure to ROFA leachate aerosols significantly enhanced the airway hyperresponsiveness in

19 OVA-sensitized mice; whereas, exposure to concentrated ambient PM (average concentration of

20 787 μg/m^3) had no effect on airway responsiveness in six separate experiments. Thus, the effect

21 of the ROFA leachate aerosols on the induction of airway hyperresponsiveness in allergic mice

22 was significantly different than that of a high concentration of concentrated ambient PM.

23 Although airway responsiveness was examined at only one post-exposure time point, these

24 findings do suggest that a great deal of caution should be used in interpreting the results of

25 studies using ROFA particles or leachates in the attempt to investigate the biologic plausibility of

26 the adverse health effects of PM.

27   Several other studies have examined in greater detail the contribution of the particle

28 component and the organic fraction of DPM to allergic asthma. Tsien et al. (1997) treated

29 transformed IgE-producing human B lymphocytes in vitro with the organic extract of DPM. The

30 organic phase extraction had no effect on cytokine production but did increase IgE production.

31 In these in vitro experiments, DPM appeared to be acting on cells already committed to IgE

1   production, thus suggesting a mechanism by which the organic fraction of combustion particles

2   can directly affect B cells and influence human allergic asthma.

3   Cultured epithelial cells from atopic asthmatics show a greater response to DPM exposure

4   when compared with cells from nonatopic nonasthmatics. IL-8, GM-CSF, and soluble ICAM-1

5   increased in response to DPM at a concentration of 10 μg/mL DPM (Bayram et al., 1998a,b).

6   This study suggests that particles could modulate airway disease through their actions on airway

7   epithelial cells. This study also suggests that bronchial epithelial cells from asthmatics are

8   different from those of nonasthmatics in regard to their mediator release in response to DPM.

9   Sagai and colleagues (1996) repeatedly instilled mice with DPM for up to 16 weeks and

10 found increased numbers of eosinophils, goblet cell hyperplasia, and nonspecific airway

11 hyperresponsiveness, changes which are central features of chronic asthma (National Institutes of

12 Health, 1997). Takano et al. (1997) extended this line of research and examined the effect of

13 repeated instillation of DPM on the antibody response to antigen (OVA) in mice. They observed

14 that antigen-specific IgE and IgG levels were significantly greater in mice repeatedly instilled

15 with both DPM and OVA. Because this upregulation in antigen-specific immunoglobulin

16 production was not accompanied by an increase in inflammatory cells or cytokines in lavage

17 fluid, it would suggest that, in vivo, DPM may act directly on immune system cells, as described

18 in the work by Tsien et al. (1997). Animal studies have confirmed that the adjuvant activity of

19 DPM also applies to the sensitization of Brown-Norway rats to timothy grass pollen (Steerenberg

20 et al., 1999).

21   Diaz-Sanchez and colleagues (1996) have continued to study the mechanism of DPM-

22 induced upregulation of allergic response in the nasal cavity of human subjects. In one study, a

23 200 μL aerosol bolus containing 0.15 mg of DPM was delivered into each naris of subjects with

24 or without seasonal allergies. In addition to increases in IgE in nasal lavage fluid (NAL), they

25 found an enhanced production of IL-4, IL-6, and IL-13, cytokines known to be B cell

26 proliferation factors. The levels of several other cytokines also were increased, suggesting a

27 general inflammatory response to a nasal challenge with DPM. In a following study, these

28 investigators delivered ragweed antigen, alone or in combination with DPM, on two occasions, to

29 human subjects with both allergic rhinitis and positive skin tests to ragweed (Diaz-Sanchez et al.

30 1997). They found that the combined challenge with ragweed antigen and DPM produced

31 significantly greater antigen-specific IgE and IgG4 in NAL. A peak response was seen at 96 h

1 postexposure. The combined treatment also induced expression of IL-4, IL-5, IL-10, and IL-13,

2 with a concomitant decrease in expression of Th1-type cytokines. Although the treatments were

3 not randomized (antigen alone was given first to each subject), the investigators reported that

4 pilot work showed no interactive effect of repeated antigen challenge on cellular and biochemical

5 markers in NAL. DPM also resulted in the nasal influx of eosinophils, granulocytes, monocytes,

6 and lymphocytes, as well as the production of various inflammatory mediators. The combined

7 DPM plus ragweed exposure did not increase the rhinitis symptoms beyond those of ragweed

8 alone. Thus, diesel exhaust (particles and gases) can produce an enhanced response to antigenic

9 material in the nasal cavity.

10   Extrapolation of these findings of enhanced allergic response in the nose to the human lung

11 would suggest that ambient combustion particles containing DPM may have significant effects

12 on allergic asthma. A study by Nordenhall et al. (2001) has addressed the effects of diesel PM on

13 airway hyperresponsiveness, lung function and airway inflammation in a group of atopic

14 asthmatics with stable disease. All were hyperresponsive to methacholine. Each subject was

15 exposed to DPM (300 μg/m^3) and air for 1 h on two separate occasions. Lung function was

16 measured before and immediately after the exposures. Sputum induction was performed 6 h, and

17 methacholine inhalation test 24 h, after each exposure. Exposure to DE was associated with a

18 significant increase in the degree of hyperresponsiveness, as compared to after air, a significant

19 increase in airway resistance and in sputum levels of interleukin (IL)-6 (p=0.048). No changes

20 were detected in sputum levels of methyl-histamine, eosinophil cationic protein,

21 myeloperoxidase, and IL-8.

22   These studies provide biological plausibility for the exacerbation of allergic asthma

23 associated with episodic exposure to PM. Although DPM may make up only a fraction of the

24 mass of urban PM, because of their small size, DPM may represent a significant fraction of the

25 ultrafine particle mode in urban air, especially in cities and countries that rely heavily on diesel-

26 powered vehicles. It must be noted that the potential contribution of DPM to the rising

27 prevalence in asthma is complicated by the fact that DPM levels have been decreasing over the

28 last decade (CALEPA report). The reported decrease in DPM levels is a result of the increased

29 combustion efficiency of diesel engines. This improvement in diesel engine design also has

30 brought about a significant decrease in the particle size of diesel emissions. Thus, the balance

1　between a decrease in diesel emissions (in terms of mass) versus the production of a smaller and

2　potentially more toxic particle size needs further exploration.

3

7.4.4　Resistance to Infectious Disease

5　　　　The development of an infectious disease requires both the presence of the appropriate

6　pathogen, as well as host susceptibility to the pathogen. There are numerous specific and

7　nonspecific host defenses against microbes, and the ability of inhaled particles to modify

8　resistance to bacterial infection could result from a decreased ability to clear or kill microbes.

9　Rodent infectivity models frequently have been used to examine the effect of inhaled particles on

10　host defense and infectivity. Mice or rats are challenged with a bacterial or viral load either

11　before or after exposure to the particles (or gas) of interest; mortality rate, survival time, or

12　bacterial clearance are then examined. A number of studies that have used the infectivity model

13　to assess the effect of inhaled PM were discussed previously (U.S. Environmental Protection

14　Agency, 1982, 1989, 1996a). In general, acute exposure to sulfuric acid aerosols at

15　concentrations up to 5,000 μg/m^3 were not very effective in enhancing mortality in a bacterially

16　mediated murine model. In rabbits, however, sulfuric acid aerosols altered anti-microbial

17　defenses after exposure for 2 h/day for 4 days to 750 μg/m^3 (Zelikoff et al., 1994). Acute or

18　short-term repeated exposures to high concentrations of relatively inert particles have produced

19　conflicting results. Carbon black (10,000 μg/m^3) was found to have no effect on susceptibility to

20　bacterial infection (Jakab, 1993); whereas a very high concentration (20,000 μg/m^3) of TiO$_2$

21　decreased the clearance of microbes and the bacterial response of lymphocytes isolated from

22　mediastinal lymph nodes (Gilmour et al., 1989a,b). In addition, exposure to DPM (2 mg/m^3,

23　7h/d, 5d/wk for 3 and 6 mo) has been shown to enhance the susceptibility of mice to the lethal

24　effects of some, but not all, microbial agents (Hahon et al., 1985). Thus, the pulmonary response

25　to microbial agents has been shown to be altered at relatively high particle concentrations in

26　animal models. Moreover, these effects appear to be highly dependent on the microbial

27　challenge and the test animal studied. Pritchard et al. (1996) observed in rats exposed to particles

28　with a high concentration of metals (e.g., ROFA), that the increased mortality rate after

29　streptococcus infection was associated with the amount of metal in the PM.

30　　　　Despite the reported association between ambient PM and deaths caused by pneumonia

31　(Schwartz, 1994), there are few recent studies that have examined the mechanisms that may be

1   responsible for the effect of PM on infectivity. In one study, Cohen and colleagues (1997)

2   examined the effect of inhaled vanadium (V) on immunocompetence. Healthy rats were

3   repeatedly exposed to 2 mg/m^3 V, as ammonium metavanadate, and then instilled with

4   polyinosinic-polycytidilic acid (poly I:C), a double-stranded polyribonucleotide that acts as a

5   potent immunomodulator. Induction of increases in lavage fluid protein and neutrophils was

6   greater in animals preexposed to V. Similarly, IL-6 and interferon-gamma were increased in

7   V-exposed animals. Alveolar macrophage function, as determined by zymosan-stimulated

8   superoxide anion production and by phagocytosis of latex particles, was depressed to a greater

9   degree after poly I:C instillation in V-exposed rats as compared to filtered air-exposed rats.

10   These findings provide evidence that inhaled V, a trace metal found in combustion particles and

11   shown to be toxic in vivo in studies using instilled or inhaled ROFA (Dreher et al., 1997;

12   Kodavanti et al., 1997b, 1999), has the potential to inhibit the pulmonary response to microbial

13   agents. It must be taken into consideration that these effects were found at very high exposure

14   concentrations of V, and as with many studies, care must be taken in extrapolating the results to

15   the ambient exposure of healthy individuals or those with preexisting cardiopulmonary disease to

16   trace concentrations (approximately 3 orders of magnitude lower concentration) of metals in

17   ambient PM.

18

19

20   **7.5 PARTICULATE MATTER TOXICITY AND PATHOPHYSIOLOGY:**
21   **IN VITRO EXPOSURES**

22   **7.5.1 Introduction**

23   Toxicological studies play an integral role in determining the biological plausibility for the

24   health effects associated with ambient PM exposure. At the time of completion of the previous

25   PM AQCD (U.S. Environmental Protection Agency, 1996a) very little was known about the

26   potential mechanisms that could explain the morbidity and mortality observed in populations

27   exposed to PM. One of the difficulties in trying to sort out possible mechanisms is the nature of

28   particles themselves. Ambient PM has diverse physicochemical properties (Table 7-9) ranging

29   from the physical characteristics of the particle to the chemical components in or on the surface

30   of the particle. Any one of these properties could change at any time in the ambient exposure

31   atmosphere, making it hard to replicate the actual properties in a controlled experiment. As a

TABLE 7-9. PHYSICOCHEMICAL PROPERTIES OF PARTICULATE MATTER

Physical Characteristics	Chemical Components
• particle mass (size, shape, density) • particle number • surface area • surface chemistry • surface charge • acidity	• elemental and organic carbon • volatile organics • metals (Fe, Cd, Co, Cu, Mn, Ni, Pb, Ti, V, Zn) • biologicals (e.g., pollen, microbes) • sulfates • nitrates • pesticides

1   result, controlled exposure studies as yet have not been able to unequivocally determine the

2   particle properties and the specific mechanisms by which ambient PM may affect biological

3   systems.

4   Despite these underlying difficulties, a larger number of toxicological studies have become

5   available since 1996 to help explain how ambient particles may exert toxic effects on the

6   cardiovascular and respiratory systems. The following section discusses the more recently

7   published studies that provide an approach toward identifying potential mechanisms by which

8   PM mediates health effects. The remaining sections discuss potential mechanisms in relation to

9   PM characteristics based on these available data.

10

11   7.5.2 Experimental Exposure Data

12   In vitro exposure is a useful technique to provide information on potential hazardous PM

13   constituents and mechanisms of PM injury, especially when only limited quantities of the test

14   material are available. In addition, in vitro exposure allows the examination of the response to

15   particles in only one or two cell types. Respiratory epithelial cells that line the airway lumen,

16   constitute the initial targets of airborne pollutants. These cells have been featured in numerous

17   studies involving airborne pollutants and show inflammatory responses similar to that of human

18   primary epithelial cultures. Limitations of in vitro studies include difficulty in extrapolating

19   dose-response relationships and from in vitro to in vivo biological response and mechanistic

20   extrapolations. In addition to alterations in physiochemcial characteristics of PM because of the

21   collection and resuspension processes, these exposure conditions do not simulate the air-cell

1   interface that actually exists within the lungs, and, thus, the exact dosage delivered to target cells

2   in vivo is not known. Furthermore, unless an in vitro exposure system that is capable of

3   delivering particles uniformly to monolayers of airway epithelial cells cultured in an air-liquid

4   interface system is used (Chen et al., 1993), the conventional incubation system alters the

5   microenvironment surrounding the cells and may alter the mechanisms of cellular injury induced

6   by these agents.

7   Even with these limitations, in vitro studies do provide an approach to identify potential

8   cellular and molecular mechanisms by which PM mediates health effects. These mechanisms

9   can then be evaluated in vivo. In vitro studies are summarized in Table 7-10.

10

11   **7.5.2.1 Ambient Particles**

12   Several studies have exposed airway epithelial cells, alveolar macrophages, or blood

13   monocytes and erythrocytes to aqueous extracts of ambient PM to investigate cellular processes

14   such as oxidant generation and cytokine production that may contribute to the pathophysiological

15   response seen in vivo. Among the ambient PM being examined were samples collected from

16   Boston, MA, (Goldsmith et al., 1998); North Provo, UT (Ghio et al., 1999a,b); St. Louis, MO

17   (SRM 1648, Dong et al., 1996; Becker and Soukup, 1998); Washington, DC (SRM 1649, Becker

18   and Soukup, 1998); Ottawa, Canada (EHC-93, Becker and Soukup, 1998); Dusseldorf and

19   Duisburg, Germany (Hitzfeld et al., 1997), Mexico City (Bonner et al., 1998), Terni, Italy

20   (Fabiani et al., 1997); and Rome, Italy (Diociaiuti et al., 2001). In any in vitro studies, however,

21   there is a potential for contamination of ambient PM by biologic material during collection on

22   filters. Endotoxin contamination, in particular, can occur at any time in the manufacture of the

23   filter media or during handling of the filter samples before, during, and after the particle

24   collection process. This potential inadvertent contamination of filter samples can make

25   extrapolation of the study results difficult, although careful handling, characterization, and

26   controls can eliminate these concerns.

27   Because soluble metals of ambient surrogates like ROFA have been associated with

28   biological effect and toxicity, several studies have investigated whether the soluble components

29   of ambient PM may have the same biological activities. Extracts of ambient PM samples

30   collected from North Provo, UT, (during 1981 and 1982) were used to test whether the soluble

31   components or ionizable metals, which accounted for approximately 0.1% of the mass, are

TABLE 7-10. IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human bronchial epithelial cells, asthmatic (ASTH) nonasthmatic (NONA)	DPM	In vitro	10-100 μg/mL	0.4 μm	2, 4, 6, 24 h	DPM caused no gross cellular damage. Ciliary beat frequency was attentuated at all doses. DPM caused IL-8 release at lower dose in ASTH than NONA. Higher concentrations of DPM suppressed IL-8, GM-CSF, and RANTES in ASTH cells.	Bayram et al. (1998a)
Human bronchial epithelial cells (smokers)	DPM	In vitro	10-100 μg/mL	0.4 μm	24 h	DPM attenuated ciliary beating. Release of IL-8, protein, GM-CSF, and SICAM-1 increased after DPM exposure.	Bayram et al. (1998b)
Human and rat AM	Four Urban air particles: ROFA DPM Volcanic ash Silica	In vitro exposure, 2×10^5 cells exposed for 2 h	Urban and DPM: 12, 27, 111, 333, or 1000 μg/mL SiO$_2$ and TiO$_2$: 4, 12, 35, or 167 μg/mL Fe$_2$O$_3$: 1:1, 3:1; 10:1 particles/cell ratio	Urban particles: 0.3-0.4 μm DPM: 0.3 μm ROFA: 0.5 μm Volcanic ash: 1.8 μm Silica: 05-10 μm TiO$_2$: <5 μm Latex: 3.8 μm	2 h for cytotoxicity, 16-18 h for cytokine assay; chemiluminescence at 30 minutes	UAP-induced cytokine production (TNF, IL-6) in AM of both species that is not related to respiratory burst or transition metals but may be related to LPS (blocked by polymyxin B but not DEF) ROFA induced strong chemiluminescence but had weak effects on TNF production.	Becker et al. (1996)
Human AM and blood monocytes	Urban air particles; St. Louis SRM 1648; Washington, DC, SRM 1649; Ottawa, Canada, EHC-93	In vitro	33 or 100 μg/mL	0.2 to 0.7 μm	3, 6, or 18-20 h	Phagocytosis was inhibited by UAP at 18 h. UAP caused decreased expression of β_2-integrins involved in antigen presentation and phagocytosis.	Becker and Soukup (1998)
Rat AM	PM$_{10}$ Mexico City 1993; volcanic ash (MSHA)	In vitro	1-100 μg/mL	<10 μm	24 h	PM$_{10}$ stimulated alveolar macrophages to induce up-regulation of PDGF $\propto$ receptor on myofiboroblasts. Endotoxin and metal components of PM$_{10}$ stimulate release of IL-β. This is a possible mechanism for PM$_{10}$-induced airway remodeling.	Bonner et al. (1998)
NHBE cells	ROFA	In vitro	0, 50, or 200 μg/mL		Analysis at 2 and 24 h postexposure	Increase in expression of the cytokines IL-6, IL-8, and TNF-α; inhibition by DMTU or deferoxamine.	Carter et al. (1997)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human erythrocytes; RAW 264.7 cells	$PM_{10-2.5}$; $PM_{2.5}$ from Rome, Italy	In vitro	50 ± 45 $\mu g/m^3$ 31 ± 24 $\mu g/m^3$ 19 ± 20 $\mu g/m^3$	PM_{10} $PM_{2.5}$ $PM_{10-2.5}$	1 h 24 h	Oxidative stress on cell membranes is related to PM surface per volume unit of suspension; small particles are more effective at decreasing viability and increasing markers of inflammation.	Diociaiuti et al. (2001)
Supercoiled DNA	PM_{10} from Edinburgh, Scotland	In vitro	996.2 ± 181.8 μg/filter in 100 μL	PM_{10}	8 h	PM_{10} caused damage to DNA; mediated by hydroxyl radicals (inhibited by mannitol) and iron (inhibited by DEF). Clear supernatant has all of the suspension activity. Free radical activity is derived either from a fraction that is not centrifugeable on a bench centrifuge or that the radical generating system is released into solution.	Donaldson et al. (1997)
Rat AM	UAP DPM	In vitro	50 to 200 $\mu g/mL$	DPM: $1.1 - 1.3$ μm UAP: St Louis, between 1974 and 1976 in a baghouse, sieved through 200-mesh (125 μm)	2 h exposure; supernatant collected 18 h postexposure	Dose dependent increase in TNF-α, IL-6, CINC, MIP-2 gene expression by urban particles but not with DPM; cytokine production were not related to ROS; cytokine production can be inhibited by polymyxin B; LPS was detected on UAP but not DPM; endotoxin is responsible for the cytokine gene expression induced by UAP in AM..	Dong et al. (1996)
Primary cultures of RTE	ROFA	In vitro		1.95 μm MMAD	Analysis at 6 and 24 h	Particle induced epithelial-cell detachment and lytic cell injury; alterations in the permeability of the cultured RTE cell layer; increase in LDH, G-6-PDH, gluathione reductase, glutathione S-transferase; mechanism of ROFA-induced RTE cytotoxicity and pulmonary cellular inflammation involves the development of an oxidative burden.	Dye et al. (1997)
Primary cultures of RTE	ROFA; metal solutions	In vitro	5, 10, or 20 $\mu g/m^2$	1.95 μm MMAD	Analysis at 6 and 24 h	Over 24 h ROFA, V, or Ni + V, but not Fe or Ni, increased epithelial permeability, decreased cellular glutathione, cell detachment, and lytic cell injury; treatment with DMTU inhibited expression of MIP-2 and IL-6 genes.	Dye et al. (1999)
Peripheral blood monocytes	Organic extract of TSP, Italy	In vitro	42.5 μg extract/m^3 (acetone)	N/A, collected from high-volume sampler (60 m^3/h)	2 h	Superoxide anion generation was inhibited at a particulate concentration of 0.17 mg/mL when stimulated with PMA; 50% increase in LDH; disintegration of plasma membrane.	Fabiani et al. (1997)
BEAS-2B	Provo PM_{10} extract	In vitro	125, 250, 500 $\mu g/mL$	PM_{10}	2 and 24 h	Dose-dependent increase in IL-6 and IL-8 produced by particles collected while the steel mill was in operation; particles collected during plant closure had the lowest concentrations of soluble Fe, Cu, And Zn	Frampton et al. (1999)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat AM	ROFA, iron sulfate, nickel sulfate, vanadyl sulfate Latex particles with metal complexed on the surface	In vitro (0.7×10^6 cells/mL)	0.01–1.0 mg/mL	3.6 μm MMAD	Up to 400 min	Increase chemiluminescence, inhibited by DEF and hydroxyl radical scavengers; solutions of metal sulfates and metal-complexed latex particles similarly elevated chemiluminescence in a dose- and time-dependent manner.	Ghio et al. (1997a)
NHBE BEAS-2B	ROFA	In vitro	5–200 μg/mL	3.6 μm	2 and 24 h	mRNA for ferritin did not change; ferritin protein increase; mRNA for transferrin receptor decreased, mRNA for lactoferrin increased; transferrin decreased whereas lactoferrin increased; deferoxamine alone increased lactoferrin mRNA.	Ghio et al. (1998c)
BEAS-2B respiratory epithelial cells	ROFA	In vitro	100 μg/mL	N/A	$\approx$1 h	Lactoferrin binding with PM metal occurred within 5 min. V and Fe [III], but not Ni, increased the concentration of lactoferrin receptor.	Ghio et al. (1999b)
BEAS-2B	Provo TSP soluble and insoluble extract	In vitro	500 μg/mL	TSP	24 h	Water soluble fraction caused greater release of IL-than insoluble fraction. The effect was blocked by deferoxamine and presumably because of metals (Fe, Cu, Zn, Pb).	Ghio et al. (1999a)
ØX174 RF1 DNA	PM_{10} from Edinburgh, Scotland	In vitro	3.7 or 7.5 μg/mL	PM_{10}	8 h	Significant free radical activity on degrading supercoiled DNA; mainly because of hydroxyl radicals (inhibited by mannitol); Fe involvement (DEF-B conferred protection); more Fe^{3+} was released compared to Fe^{2+}, especially at pH 4.6 than at 7.2.	Gilmour et al. (1996)
Hamster AM	ROFA or CAPs	In vitro	0, 25, 50, 100, or 200 μg/mL	CAPs: 0.1–2.5 μm (from Harvard concentrator) TiO_2: 1 μm	30 min incubation, analysis immediately following	Dose-dependent increase in AM oxidant stress with both ROFA and CAP. Increase in particle uptake; Mac-type SR mediate a substantial proportion of AM binding; particle-associated components (e.g., transition metals) are likely to mediate intracellular oxidant stress and proinflammatory activation.	Goldsmith et al. (1997)
Hamster AM	CAPs, ROFA, and their water-soluble and particulate fractions	In vitro	0-200 mg/mL	CAPs = 0.125 μm ROFA = 1.0 μm	30 min	ROFA and CAPs (water soluble components) caused increases in DCFH oxidation; CAPs samples and components showed substantial day-to-day variability in their oxidant effects; ROFA increased MIP-2 and TNF-α production in AM and can be inhibitable by NAC.	Goldsmith et al. (1998)
AMs from female CD rats	Vanadyl chloride sodium metavanadate	In vitro	10-1000 μm metavanadate	N/A	30 min	Metavanadate caused increased production of ROS. The LOEL was 50 μM.	Grabowski et al. (1999)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human PMN	Aqueous and organic extracts of TSP in Dusseldorf and Duisburg, Germany	In vitro	0.42–0.78 mg dust/mL	Collected by high volume sampler, 90% <5 μm, 50% <1μm, maximum at 0.3-0.45 μm Extracted using water and then dichloromethane to yield aqueous and organic extracts	Up to 35 min	PM extract alone significantly stimulated the production and release of ROS in resting but not in zymosan-stimulated PMN. The effects of the PM extracts were inhibited by SOD, catalase and sodium azide (NaN$_3$); Zymosan-induced LCL is inhibited by both types of extracts, but aqueous extracts have a stronger inhibitory effect.	Hitzfeld et al. (1997)
Human AM	UAP (#1648, 1649) Volcanic ash ROFA	In vitro	0, 25, 100, or 200 μg/mL	Volume median diameter: ROFA 1.1 μm #1648: 1.4 μm #1649: 1.1 μm volcanic ash 2.3 μm	24 h	ROFA highly toxic; urban PM toxic at 200μg/mL; ROFA produced significant apoptosis as low as 25 μg/mL; UAP produced apoptosis at 100 μg/mL; UAP and ROFA also affect AM phenotype: increased immune stimulatory, whereas decreased immune suppressor phenotype.	Holian et al. (1998)
Primary GPTE cells	ROFA DOFA STL WDC OT MSH	In vitro	6-25, 12.5, 25, and 50 μg/cm^3	N/A	4, 8, and 24 h	ROFA was the most toxic particle, enhancing mucin secretion and causing toxicity, assessed by LDH release.	Jiang et al. (2000)
Human Bronchial Epithelial (BEAS-2B) cells	TSP collected in Provo	In vitro	TSP filter samples (36.5 mg/mL) agitated in deionized H$_2$O$_2$ for 96 h, centrifuged at 1200g for 30 min, lyophylized and resuspended in deionized H$_2$O$_2$ or saline	N/A (TSP samples, comprised 50 to 60% PM$_{10}$)	Sacrificed at 24 h	Provo particles caused cytokine-induced neutrophil-chemoattractant-dependent inflammation of rat lungs; Provo particles stimulated IL-6 and IL-8 production, increased IL-8 mRNA and ICAM-1 in BEAS-2B cells, and stimulated IL-8 secretion in primary cultures of BEAS-2B cells; cytokine secretion was preceded by activation of NF-κB and was reduced by SOD, DEF, or NAC; quantities of Cu^{2+} found in Provo particles replicated the effects	Kennedy et al. (1998)
Rat AM	ROFA, 10 samples with differing metal composition	In vitro	0 or 50 μg/mL	1.99 - 2.55 μm MMAD	1-6 h	Macrophage activation, as determined by chemiluminescence was maximal with the V-rich particles as opposed to V plus Ni-rich particles.	Kodavanti et al. (1998a)
Human lung mucoepidermoid carcinoma cell line, NCI-H292	ROFA	In vitro	30 μg/ml	N/A	1 h	Epithelial cells secreted increased mucin and lysozyme; effect caused by V-rich fraction (18.8%).	Longphre et al. (2000)
BEAS-2B, airway epithelial cells	ROFA	In vitro	0, 0.5, or 2.0 mg in 10 mL	N/A	1 h	ROFA induced production of acetaldehyde in dose-dependant fashion.	Madden et al. (1999)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Male (Wistar) rat lung macrophages	Urban dust SRM 1649, TiO_2, quartz	In vitro	0-100 μg in 1 mL	N/A	18 h	Cytotoxicity ranking was quartz > SRM 1649 > TiO_2, based on cellular ATP decrease and LDH, acid phosphatase, and β-glucuronidase release.	Nadeau et al. (1996)
Human blood monocytes and neutrophils (PMN)	Ambient air particles, carbon black, oil fly ash, coal fly ash	In vitro	100 μg in 0.2 mL	N/A	40 min.	ROS generation, measured by LCL increased in PMN, was correlated with Si, Fe, Mn, Ti, and Co content but not V, Cr, Ni, and Cu. Deferoxamine, a metal ion-chelator, and did not affect LCL in PMN, suggesting that metal ions are not related to the induction of LCL.	Prahalad et al. (1999)
Human airway epithelium-derived cell lines BEAS-2B (S6-subclone)	ROFA	In vitro	0, 6, 12, 25, or 50 μg/mL	1.96 μm	1 and 24 h	Activation of IL-6 gene by NF-κB activation and binding to specific sequences in promoter of IL-6 gene; inhibition of NF-κB activation by DEF and NAC; increase in PGE_2, IL-6, TNF, and IL-8; activation NF-B may be a critical first step in the inflammatory cascade following exposure to ROFA particles.	Quay et al. (1998)
Human airway epithelium-derived cell line BEAS 2B	ROFA	In vitro	2, 20, or 60 μg/cm^2	1.96 μm	24-h exposure	Epithelial cells exposed to ROFA for 24 h secreted substantially increased amounts of the PHS products prostaglandins E_2 and $F_{2\alpha}$; ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in PHS activity.	Samet et al. (1996)
Human airway epithelium-derived cell line BEAS	ROFA Synthetic ROFA (soluble Ni, Fe, and V)	In vitro	ROFA: 0–200 μg/mL Synthetic ROFA (100μg/mL): Ni, 64 μM Fe, 63 μM V, 370 mM	ROFA: 1.96 μm Synthetic ROFA: N/A (soluble)	Up to 24 h	Tyrosine phosphatase activity, which was known to be inhibited by vanadium ions, was markedly diminished after ROFA treatment; ROFA exposure induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in BEAS cells.	Samet et al. (1997)
Human airway epithelium-derived cell lines BEAS-2B	Particle components As, Cr, Cu, Fe, Ni, V, and Zn	In vitro	500 μM of As, F, Cr (III), Cu, V, Zn	N/A (soluble)	20 min and 6 and 24 h	Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells; activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK under these conditions; the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn; acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells.	Samet et al. (1998)
A549 ØX174 RFI DNA	Urban particles: SRM 1648, St. Louis SRM 1649, Washington, DC	In vitro	1 mg/mL for Fe mobilization assay	SRM 1648: 50% < 10 μm SRM 1649: 30% < 10 μm	Up to 25 h	Single-strand breaks in DNA were induced by PM only in the presence of ascorbate, and correlated with amount of Fe that can be mobilized; ferritin in A549 cells was increased with treatment of PM suggesting mobilization of Fe in the cultured cells.	Smith and Aust (1997)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.[a]	Particle or Constituent[b]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human AMs	Provo PM_{10} extract	In vitro	500 μg	PM_{10}	24 h	AM phagocytosis of (FITC)-labeled Saccharomyces cerevisiae inhibited 30% by particles collected before steel mill closure.	Soukup et al. (2000)
Human AMs	Chapel Hill PM extract; both H_2O soluble(s) and insoluble(is)	In vitro	100 μg/mL	$PM_{2.5}$ $PM_{10-2.5}$	24 h	Increased cytokine production (IL-6, TNFα, MCP-1); $_{is}PM_{10} > {}_sPM_{10} > {}_{is}PM_{2.5}$; $_sPM_{2.5}$ was inactive; endotoxin was partially responsible.	Soukup and Becker (2001)
Rat (Wistar) AM RAM cells (a rat AM cell line)	TiO_2	In vitro	20, 50, or 80 μg/mL	N/A	4 h	Opsonization of TiO_2 with surfactant components resulted in a modest increase in AM uptake compared with that of unopsonized TiO_2; surfactant components increase AM phagocytosis of particles.	Stringer and Kobzik (1996)
A549	ROFA, α-quartz, TiO_2	In vitro	1 mg/mL	N/A	60 min	Exposure of A549 cells to ROFA, α-quartz, but not TiO_2, caused increased IL-8 production in TNF-α primed cells in a concentration-dependent manner.	Stringer and Kobzik (1998)
A549	TiO_2, Fe_2O_3, CAP, and the fibrogenic particle α-quartz	In vitro	TiO_2 [40 μg/mL], Fe_2O_3 [100 μg/mL], α-quartz [200 μg/mL], or CAP [40 μg/mL]	N/A	24 h	$TiO_2 > Fe_2O_3 > \alpha$-quartz $>$ CAP in particle binding; binding of particle was found to be calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was calcium-independent; scavenger receptor, mediate particulate binding; α-quartz, but not TiO_2 or CAP, caused a dose-dependent production of IL-8.	Stringer et al. (1996)
RLE-6TN cells (type II like cell line)	$PM_{2.5}$, Burlington, VT; Fine/ultrafine TiO_2	In vitro	1, 2.5, 5, or 10 μg/mL	$PM_{2.5}$: 39 nm Fine TiO_2: 159 nm UF TiO_2: 37 nm	24 and 48 h exposure	Increases in c-Jun kinase activity, levels of phosphorylated c-Jun immunoreactive protein, and transcriptional activation of activator protein-1-dependent gene expression; elevation in number of cells incorporating 5'-bromodeoxyuridine.	Timblin et al. (1998)
Rat, Long Evans epithelial cells	CFA PFA α-quartz.			2.6 μm 17.7 μm 2.5 μm	3 h	CFA produced highest level of hydroxyl radicals; iron content is more important than quartz content.	Van Maanen et al. (1999)
BEAS-2B human bronchial epithelial cells	ROFA Birmingham, AL. 188 mg/g of VO	In vitro	100 μg/mL	N/A	2-6 h	ROFA caused increased intracellular Ca^{++}, IL-6, IL-and TNF-α through activation of capsicin- and pH-sensitive receptors.	Veronesi et al. (1999b)
NHBE BEAS-2B	Provo PM_{10} extract	In vitro	50, 100, 200 μg/mL	PM_{10}	24 h	Dose-dependent increase in expression of IL-8 produced by particles collected when the steel mill was in operation.	Wu et al. (2001)

[a]Cell types: RTE = Rat tracheal epithelial cells; GPTE = Guinea pig tracheal epithelial cells
[b]Particles: See Table 7-1

responsible for the biological activity of the extracted PM components. The oxidant generation (thiobarbituric acid reactive products), release of IL-8 from BEAS-2B cells, and PMN influx in rats exposed to these samples correlated with sulfate content and the ionizable concentrations of metals in these PM extracts (Ghio et al., 1999a,b). In addition, these extracts stimulated IL-6 and IL-8 production as well as increased IL-8 mRNA and enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in BEAS-2B cells (Kennedy et al., 1998). Cytokine secretion was preceded by activation of nuclear factor kappa B (NF-κB) and was reduced by treatment with superoxide dismutase (SOD), Deferoxamine (DEF), or N-acetylcysteine. The addition of similar quantities of Cu^{+2} as found in the Provo extract replicated the biological effects observed with particles alone. When normal constituents of airway lining fluid (mucin or ceruloplasmin) were added to BEAS cells, particulate-induced secretion of IL-8 was modified. Mucin reduced IL-8 secretion; whereas ceruloplasmin significantly increased IL-8 secretion and activation of NF-κB. The authors suggest that copper ions may cause some of the biologic effects of inhaled PM in the Provo region and may provide an explanation for the sensitivity of asthmatics to Provo PM seen in epidemiologic studies.

Frampton et al. (1999) examined the effects of the same ambient PM samples collected from Utah Valley in the late 1980s (see Section 7.2.1). Aqueous extracts of the filters were analyzed for metal and oxidant production and added to cultures of human respiratory epithelial cells (BEAS-2B) for 2 or 24 h. Particles collected in 1987, when the steel mill was closed had the lowest concentrations of soluble iron, copper, and zinc and showed the least oxidant generation. Ambient PM collected before and after plant closing induced expression of IL-6 and IL-8 in a dose-response relationship (125, 250, and 500 μg/mL). Ambient PM collected after reopening of the steel mill also caused cytotoxicity, as demonstrated by microscopy and LDH release at the highest concentration used (500 μg/mL).

Soukup et al. (2000) used similar ambient PM extracts as Frampton et al. (1999) to examine effects on human alveolar macrophages. The phagocytic activity and oxidative response of AMs was measured after segmental instillation of aqueous extracts from the Utah Valley or after overnight in vitro cell culture. Ambient PM collected before closure of the steel mill inhibited AM phagocytosis of (FITC)-labeled *Saccharomyces cerevisiae* by 30%; no significant effect on phagocytosis was seen with the other two extracts. Furthermore, although extracts of ambient PM collected before and after plant closure inhibited oxidant activity of AMs when

1   incubated overnight in cell culture, only the former particles caused an immediate oxidative

2   response in AMs. Host defense effects were attributed to apoptosis which was most evident in

3   particles collected before plant closure. Interpretation of loss of these effects by chelation

4   removal of the metals was complicated by the observed differences in apoptosis despite similar

5   metal contents of ambient PM collected during the steel mill operation.

6   Wu et al (2001) investigated the intracellular signaling mechanisms for the pulmonary

7   responses to Utah Valley PM extracts. Human primary airway epithelial cells were exposed to

8   aqueous extracts of PM collected from the year before, during, and after the steel mill closure in

9   Utah Valley. Transfection with kinase-deficient extracellular signal-regulated kinase (ERK)

10 constructs partially blocked the PM-induced interleukin (IL)-8 promoter reporter activity. The

11 mitogen-activated protein kinase/ERK kinase (MEK) activity inhibitor PD-98059 significantly

12 abolished IL-8 released in response to the PM, as did the epidermal growth factor (EGF) receptor

13 kinase inhibitor AG-1478. Western blotting showed that the PM-induced phosphorylation of

14 EGF receptor tyrosine, MEK1/2, and ERK1/2 could be ablated with AG-1478 or PD-98059. The

15 results indicate that the potency of Utah Valley PM collected during plant closure was lower than

16 that collected while the steel mill was in operation and imply that Utah Valley PM can induce IL-

17 8 expression partially through the activation of the EGF receptor signaling.

18   There are regional as well as daily variations in the composition of ambient PM and, hence,

19 its biological activities. For example, concentrated ambient PM (CAP, from Boston urban air)

20 has substantial day-to-day variability in its composition and oxidant effects (Goldsmith et al.,

21 1998). Similar to Utah PM, the water-soluble component of Boston CAPs significantly

22 increased AM oxidant production and inflammatory cytokine (MIP2 and TNFα) production over

23 negative control values. These effects can be blocked by metal chelators or antioxidants. The

24 regional difference in biological activity of ambient PM has been shown by Becker and Soukup

25 (1998). The oxidant generation, phagocytosis, as well as the expressions of receptors important

26 for phagocytosis in human alveolar macrophage and blood monocyte were reduced significantly

27 by PM exposure.

28   Becker and Soukup (1998) and others (Dong et al., 1996, Becker et al., 1996) have

29 suggested that the biological activity of the ambient PM may result from the presence of

30 endotoxin on the particles rather than metal-associated oxidant generation. Using the same urban

31 particles (SRM 1648), cytokine production (TNF-α, IL-1, Il-6, CINC, and MIP-2) was increased

1   in macrophages following treatment with 50 to 200 μg/mL of urban PM (Dong et al., 1996). The

2   urban particle-induced TNF-α secretion was abrogated completely by treatment with polymyxin

3   B, an antibiotic that blocks LPS-associated activities, but not with antioxidants.

4   The involvement of endotoxin, at least partially, in PM induced biological effects was

5   supported more recently by Bonner et al. (1998) and Soukup and Becker (2001). Urban PM_{10}

6   collected from north, south, and central regions of Mexico City was used with SD rat AM to

7   examine PM effects on platelet-derived growth factor (PDGF) receptors on lung myofibroblasts

8   (Bonner et al., 1998). Mexico City PM_{10} (but not volcanic ash) stimulated secretion of

9   upregulatory factors for the PDGF α receptor, possibly via IL-1β. In the presence of an

10   endotoxin-neutralizing protein, the Mexico City PM_{10} effect on PDGF was blocked partially,

11   suggesting that LPS was responsible partially for the effect of the PM_{10} on macrophages.

12   In addition, both LPS and vanadium (both present in the PM_{10}) acted directly on lung

13   myofibroblasts. However, the V levels in Mexico City PM_{10} were probably not high enough to

14   exert an independent effect. The authors concluded that PM_{10} exposure could lead to airway

15   remodeling by enhancing myofibroblast replication and chemotaxis.

16   Soukup and Becker (2001) collected fresh $PM_{2.5}$ and $PM_{10-2.5}$ from the ambient air of

17   Chapel Hill, NC, and compared the activity of these two particle size fractions. Both water

18   soluble and insoluble components were assessed for cytokine production, inhibition of

19   phagocytosis, and induction of apoptosis. The most potent fraction was the insoluble $PM_{10-2.5}$.

20   Endotoxin was responsible for much of the cytokine production, while inhibition of phagocytosis

21   was induced by other moieties in the coarse material. None of the activities were inhibited by the

22   metal chelator deferoxamine.

23   The effects of water soluble as well as organic components (extracted in dichloromethane)

24   of ambient PM were investigated by exposing human PMN to PM extracts (Hitzfeld et al., 1997).

25   PM was collected with high-volume samplers in two German cities, Dusseldorf and Duisburg;

26   these sites have high traffic and high industrial emissions, respectively. Organic, but not

27   aqueous, extracts of PM alone significantly stimulated the production and release of ROS in

28   resting human PMN. The effects of the PM extracts were inhibited by SOD, catalase, and

29   sodium azide (NaN_3). Similarly, the organic fraction (extractable by acetone) of ambient PM

30   from Terni, Italy, had been shown to produce cytotoxicity, superoxide release in response to

31   PMA and zymosan in peripheral monocytes (Fabiani et al., 1997).

1   Diociaiuti et al. (2001) compared the in vitro toxicity of coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$)

2   particulate matter, collected in an urban area of Rome. The in vitro toxicity assays used included

3   human red blood cell hemolysis, cell viability, and nitric oxide (NO) release in the RAW 264.7

4   macrophage cell line. There was a dose-dependent hemolysis in human erythrocytes when they

5   were incubated with fine and coarse particles. The hemolytic potential was greater for the fine

6   particles than for the coarse particles in equal mass concentration. However, when data were

7   expressed in terms of PM surface area per volume of suspension, the hemolytic activity of the

8   fine fraction was equal to the coarse fraction. This result suggested that the oxidative stress

9   induced by PM on the cell membranes could be due mainly to the interaction between the particle

10   surfaces and the cell membranes. Although RAW 264.7 cells challenged with fine and coarse

11   particles showed decreased viability and an increased release of NO, a key inflammatory

12   mediator, both effects were not dose-dependent in the tested concentration range. The fine

13   particles were the most effective in inducing these effects when the data were expressed as mass

14   concentration or as surface area per unit volume. The authors concluded that these differences in

15   biological activity were due to the different physicochemical natures of the particles.

16

17   **7.5.2.2 Comparison of Ambient and Combustion-Related Surrogate Particles**

18   In vitro toxicology studies utilizing alveolar macrophages as target cells (Imrich et al.,

19   2000; Long et al., 2001; Ning et al., 2000; Mukae et al., 2000, 2001; van Eeden et al., 2001) have

20   found that urban air particles are much more potent for inducing cellular responses than

21   individual surrogate combustion particles such as diesel and ROFA. Similar to the results

22   described above in Section 7.5.2.1, these studies also show that when cytokine responses are

23   measured, LPS/endotoxin is found to be responsible for most of the activity. Metals, on the other

24   hand, do not seem to affect cytokine production, as confirmed by studies showing that ROFA

25   does not induce macrophage cytokine production. These results are important because LPS is an

26   important component associated with both coarse and fine mode particles (Menetrez et al., 2001).

27   In fact, in one study (Long et al., 2001), cytokine responses in the alveolar macrophages were

28   correlated with LPS content and more LPS was found associated with indoor $PM_{2.5}$ than outdoor

29   $PM_{2.5}$.

30   Imrich et al., (2000) found that when mice alveolar macrophages were stimulated with

31   CAPs ($PM_{2.5}$), the resulting TNF responses could be inhibited by the use of an endotoxin

neutralizing agent [e.g., polymyxin-B (PB)]. Because the MIP-2 response (IL-8) was only partly

inhibited by PB; however, the authors concluded that endotoxin primed cells to respond to other

particle components. In a related study (Ning et al., 2000), the use of PB showed that particle-

absorbed endotoxin in CAPs suspensions caused activation of normal (control) AMs, while other

(nonendotoxin) components were predominantly responsible for the enhanced cytokine release

observed by primed AMs incubated with CAPs. The non-LPS component was not identified in

this study, however, the AM biological response did not correlate with any of a panel of elements

quantified within the insoluble CAPs samples (e.g., Al, Cd, Cr, Cu, Fe, Mg, Mn, Ni, S, Ti, V).

Van Eeden et al. (2001) compared ROFA, the atmospheric dust sample EHC-93, and

different size latex particles for cytokine induction on human alveolar macrophages. The

EHC-93 particles produced greater than 8-fold induction of various cytokines, including IL-1,

TNF, GMCSF; the other particles induced these cytokines approximately 2-fold. Using the same

EHC-93 particles, Mukae et al. (2000, 2001) found that inhalation exposure stimulated bone

marrow band cell-granulocyte precursor production. They also found that the magnitude of the

response was correlated with the amount of phagocytosis of the particles by alveolar

macrophages. These results may indicate that macrophages produce factors which stimulate

bone marrow, including IL-6 and GMCSF. In fact, alveolar macrophages exposed in vitro to

these particles released cytokines; and when the supernatant of PM-stimulated macrophages was

instilled into rabbits, the bone marrow was stimulated.

In a series of studies using the same ROFA samples, several in vitro experiments have

investigated the biochemical and molecular mechanisms involved in ROFA induced cellular

injury. Prostaglandin metabolism in cultured human airway epithelial cells (BEAS-2B and

NHBE) exposed to ROFA was investigated by Samet et al. (1996). Epithelial cells exposed to

ROFA for 24 h secreted substantially increased amounts of prostaglandins E2 and F2 α. The

ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in

activity of the PHS-2 form of prostaglandin H synthase as well as mRNA coded for this enzyme.

In contrast, expression of the PHS1 form of the enzyme was not affected by ROFA treatment of

airway epithelial cells. These investigators further demonstrated that noncytotoxic levels of

ROFA induced a significant dose- and time-dependent increase in protein tyrosine phosphate, an

important index of signal transduction activation leading to a broad spectrum of cellular

responses. ROFA-induced increases in protein phosphotyrosines were associated with its soluble

1   fraction and were mimicked by V-containing solutions but not iron or nickel solutions (Samet

2   et al., 1997).

3   ROFA also stimulates respiratory cells to secrete inflammatory cytokines such as IL-6,

4   IL-8, and TNF. Normal human bronchial epithelial (NHBE) cells exposed to ROFA produced

5   significant amounts of IL-8, IL-6, and TNF, as well as mRNAs coding for these cytokines (Carter

6   et al., 1997). Increases in cytokine production were dose-dependent. The cytokine production

7   was inhibited by the addition of metal chelator, DEF, or the free radical scavenger

8   dimethylthiourea (DMTU). Similar to the data of Samet et al. (1997), V but not Fe or Ni

9   compounds were responsible for these effects. Cytotoxicity, decreased cellular glutathione levels

10   in primary cultures of rat tracheal epithelial (RTE) cells exposed to suspensions of ROFA

11   indicated that respiratory cells exposed to ROFA were under oxidative stress. Treatment with

12   buthionine sulfoxamine (an inhibitor of γ-glutamyl cysteine synthetase) augmented ROFA-

13   induced cytotoxicity; whereas treatment with DMTU inhibited ROFA-induced cytoxicity further

14   suggested that ROFA-induced cell injury may be mediated by hydroxyl-radical-like reactive

15   oxygen species (ROS) (Dye et al., 1997). Using BEAS-2B cells, a time- and dose-dependent

16   increase in IL-6 mRNA induced by ROFA was shown to be preceded by the activation of nuclear

17   proteins, for example, nuclear factor-κB (NF-κB) (Quay et al., 1998). Taken together, ROFA

18   exposure increases oxidative stress, perturbs protein tyrosine phosphate homeostasis, activates

19   NF-κB, and up-regulates inflammatory cytokine and prostaglandin synthesis and secretion to

20   produce lung injury.

21   Stringer and Kobzik (1998) observed that "primed" lung epithelial cells exhibited enhanced

22   cytokine responses to PM. Compared to normal cells, exposure of tumor necrosis factor (TNF)-

23   α-primed A549 cells to ROFA or α-quartz caused increased IL-8 production in a concentration-

24   dependent manner for particle concentrations ranging from 0-200 μg/mL. Addition of the

25   antioxidant N-acetylcysteine (NAC) (1.0 mM) decreased ROFA and α-quartz-mediated IL-8

26   production by approximately 50% in both normal and TNF-α-primed A549 cells. Exposure of

27   A549 cells to ROFA caused an increase in oxidant levels that could be inhibited by NAC. These

28   data suggest that (1) lung epithelial cells primed by inflammatory mediators show increased

29   cytokine production after exposure to PM and (2) oxidant stress is an important mechanism for

30   this response.

1   In summary, exposure of lung epithelial cells to ambient PM or ROFA leads to increased

2   production of cytokines and the effects may be mediated, at least in part, through production of

3   ROS. Day-to-day variations in the components of PM, such as soluble transition metals, which

4   may be critical to eliciting the response, are suggested. The involvement of organic components

5   in ambient PM also was suggested in some studies.

6

7.5.3 Potential Cellular and Molecular Mechanisms

7.5.3.1 Reactive Oxygen Species

9   Ambient particulate matter contains transition metals, such as iron (most abundant),

10   copper, nickel, vanadium, and cobalt. These metals are capable of catalyzing the one-electron

11   reductions of molecular oxygen necessary to generate reactive oxygen species (ROS). These

12   reactions can be demonstrated by the iron-catalyzed Haber-Weiss reactions that follow.

13

$$\text{Reductant}^n + \text{Fe(III)} \rightarrow \text{Reductant}^{n+1} + \text{Fe(II)} \tag{1}$$

$$\text{Fe(II)} + O_2^- \rightarrow \text{Fe(III)} + O_2^- \tag{2}$$

$$HO_2^- + O_2^- + H^+ \rightarrow O_2 + H_2O_2 \tag{3}$$

$$\text{Fe(II)} + H_2O_2 \rightarrow \text{Fe(III)} + {}^{\bullet}OH + HO^- \text{ (Fenton Reaction)} \tag{4}$$

18
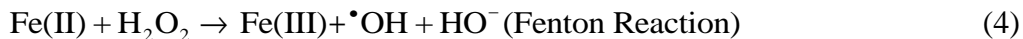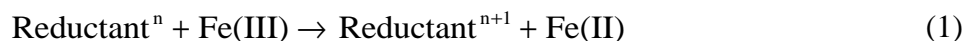
19   Iron will continue to participate in the redox cycle in the above reactions as long as there is

20   sufficient O_2 or H_2O_2 and reductants.

21   Soluble metals from inhaled PM dissolved into the fluid lining of the airway lumen can

22   react directly with biological molecules (acting as a reductant in the above reactions) to produce

23   ROS. For example, ascorbic acid in the human lung epithelial lining fluid can react with Fe(III)

24   from inhaled PM to cause single strand breaks in supercoiled plasmid DNA, ϕX174 RFI (Smith

25   and Aust, 1997). The DNA damage caused by a PM_{10} suspension can be inhibited by mannitol,

26   an hydroxyl radical scavenger, further confirming the involvement of free radicals in these

27   reactions (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997). Because the clear

28   supernatant of the centrifuged PM_{10} suspension contained all of the suspension activity, the free

29   radical activity is derived either from a fraction that is not centrifugable (10 min at 13,000 rpm

1   on a bench centrifuge) or the radical generating system is released into solution (Gilmour et al.,

2   1996; Donaldson et al., 1997; Li et al., 1997).

3   In addition to measuring the interactions of ROS and biomolecules directly, the role of

4   ROS in PM-induced lung injury also can be assessed by measuring the electron spin resonance

5   (ESR) spectrum of radical adducts or fluorescent intensity of dichlorofluorescin (DCFH), an

6   intracellular dye that fluoresces on oxidation by ROS. Alternatively, ROS can be inhibited using

7   free radical scavengers, such as dimethylthiourea (DMTU); antioxidants, such as glutathione or

8   N-acetylcysteine (NAC); or antioxidant enzymes, such as superoxide dismutase (SOD). The

9   diminished response to PM after treatment with these antioxidants may indicate the involvement

10   of ROS; however, some antioxidants (e.g., thiol-containing) can interact with metal ions directly.

11   As described earlier, Kadiiska et al. (1997) used the ESR spectra of 4-POBN [α-(4-pyridyl

12   1-oxide)-N-tert-butylnitrone] adducts to measure ROS in rats instilled with ROFA and

13   demonstrated the association between ROS production within the lung and soluble metals in

14   ROFA. Using DMTU to inhibit ROS production, Dye et al. (1997) had shown that systemic

15   administration of DMTU impeded development of the cellular inflammatory response to ROFA,

16   but did not ameliorate biochemical alterations in BAL fluid. Goldsmith et al. (1998), as

17   described earlier, showed that ROFA and CAPs caused increases in ROS production in AMs.

18   The water-soluble component of both CAPs and ROFA significantly increased AM oxidant

19   production over negative control values. In addition, increased PM-induced cytokine production

20   was inhibited by NAC. Li et al. (1996, 1997) instilled rats with PM_{10} particles (collected on

21   filters from an Edinburgh, Scotland, monitoring station). Six hours after intratracheal instillation

22   of PM_{10}, they observed a decrease in glutathione (GSH) levels in the BAL fluid. Although this

23   study does not describe the composition of the PM_{10}, the authors suggest that changes in GSH, an

24   important lung antioxidant, support the contention that the free radical activity of PM_{10} is

25   responsible for its biological activity in vivo.

26   In addition to ROS generated directly by PM, resident or newly recruited AMs or PMNs

27   also are capable of producing these reactive species on stimulation. The ROS produced during

28   the oxidative burst can be measured using a chemiluminescence (CL) assay. With this assay,

29   AM CL signals in vitro have been shown to be greatest with ROFA containing primarily soluble

30   V and were less with ROFA containing Ni plus V (Kodavanti et al., 1998a). As described

31   earlier, exposures to Dusseldorf and Duisburg PM increased the resting ROS production in

1   PMNs, which could be inhibited by SOD, catalase, and sodium azide (Hitzfeld et al., 1997).

2   Stringer and Kobzik (1998) showed that addition of NAC (1.0 mM) decreased ROFA-mediated

3   IL-8 production by approximately 50% in normal and TNF-α-primed A549 cells. In addition,

4   exposures of A549 cells to ROFA caused a substantial (and NAC inhibitable) increase in oxidant

5   levels as measured by DCFH oxidation. In human AMs, Becker et al. (1996) found a CL

6   response for ROFA, but not urban air particles (Ottawa and Dusseldorf) or volcanic ash.

7   Metal compounds of PM are the most probable species capable of catalyzing ROS

8   generation on exposure to PM. To determine elemental content and solubility in relation to their

9   ability to generate ROS, PMN or monocytes were exposed to a wide range of ambient air

10   particles from divergent sources (one natural dust, two types of oil fly ash, two types of coal fly

11   ash, five different ambient air samples, and one carbon black sample) (Prahalad et al., 1999), and

12   CL production was measured over a 20-min period postexposure. Percent of sample mass

13   accounted for by XRF detectable elements was 1.2% (carbon black); 22 to 29% (natural dust and

14   ambient air particles); 13 to 22% (oil fly ash particles); and 28 to 49% (coal fly ash particles).

15   The major proportion of elements in most of these particles were aluminosilicates and insoluble

16   iron, except oil derived fly ash particles in which soluble vanadium and nickel were in highest

17   concentration, consistent with particle acidity as measured in the supernatants. All particles

18   induced CL response in cells, except carbon black. The CL response of PMNs in general

19   increased with all washed particles, with oil fly ash and one urban air particle showing statistical

20   differences between deionized water washed and unwashed particles. These CL activities were

21   significantly correlated with the insoluble Si, Fe, Mn, Ti, and Co content of the particles.

22   No relationship was found between CL and soluble transition metals such as V, Cr, Ni, and Cu.

23   Pretreatment of the particles with a metal ion chelator, deferoxamine, did not affect CL activities.

24   Particle sulfate content and acidity of the particle suspension did not correlate with CL activity.

25   Soluble metals can be mobilized into the epithelial cells or AMs to produce ROS

26   intracellularly. Size fractionated coal fly ash particles (2.5, 2.5 to 10, and <10 μm) of bituminous

27   b (Utah coal), c (Illinois coal), and lignite (Dakota coal) were used to compare the amount of iron

28   mobilization in A549 cells and by citrate (1 mM) in cell-free suspensions (Smith et al., 1998).

29   Iron was mobilized by citrate from all three size fractions of all three coal types. More iron, in

30   Fe(III) form, was mobilized by citrate from the <2.5-μm fraction than from the >2.5-μm

31   fractions. In addition, the amount of iron mobilized was dependent on the type of coal used to

1   generate the fly ash (Utah coal > Illinois coal = Dakota coal) but not related to the total amount

2   of iron present in the particles. Ferritin (an iron storage protein) levels in A549 cells increased by

3   as much as 12-fold in cells treated with coal fly ash (Utah coal > Illinois coal > Dakota coal).

4   More ferritin was induced in cells treated with the <2.5-μm fraction than with the >2.5-μm

5   fractions. Mossbauer spectroscopy of a fly ash sample showed that the bioavailable iron was

6   assocated with the glassy aluminosilicate fraction of the particles (Ball et al., 2000). As with the

7   bioavailability of iron, there was an inverse correlation between the production of IL-8 and fly

8   ash particle size with the Utah coal fly ash being the most potent.

9   Using ROFA and colloidal iron oxide, Ghio et al. (1997b; 1998a,b,c; 1999c; 2000b) have

10   shown that exposures to these particles disrupted iron homeostasis and induced the production of

11   ROS in vivo and in vitro. Treatment of animals or cells with metal-chelating agents such as DEF

12   with an associated decrease in response has been used to infer the involvement of metal in PM-

13   induced lung injury. Metal chelation by DEF (1 mM) caused significant inhibition of particulate-

14   induced AM oxidant production, as measured using DCFH (Goldsmith et al., 1998). DEF

15   treatment also reduced NF-κB activation and cytokine secretion in a human bronchial epithelial

16   cell line (BEAS-2B cells) exposed to Provo PM (Kennedy et al., 1998). However, treatment of

17   ROFA suspension with DEF was not effective in blocking leachable metal induced acute lung

18   injury (Dreher et al., 1997). Dreher et al. (1997) indicated that DEF could chelate Fe(III) and

19   V(II), but not Ni(II), suggesting that metal interactions played a significant role in ROFA-induced

20   lung injury.

21   Other than Fe, several V compounds have been shown to increase mRNA levels for

22   selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996).

23    $NaVO_3$ and $VOSO_4$, highly soluble forms of V, tended to induce pulmonary inflammation and

24   inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble

25   form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest

26   following exposure to V_2O_5. However, metal components of fly ash have not been shown to

27   consistently increase ROS production from bovine AM treated with combustion particles

28   (Schluter et al., 1995). For example, As(III), Ni(II), and Ce(III), which are major components of

29   fly ash, had been shown to inhibit the secretion of superoxide anions (O_2^-) and hydrogen

30   peroxide. In the same study, O_2^- were lowered by Mn(II) and Fe(II); whereas V(IV) increased O_2^-

31   and H_2O_2. In contrast, Fe(III) increase O_2^- productions, demonstrating that the oxidation state of

1   metal may influence its oxidant generating properties. Other components of fly ash, such as

2   Cd(II), Cr(III), and V(V), had no effects on ROS.

3   It is likely that a combination of several metals rather than a single metal in PM is

4   responsible for the PM induced cellular response. For example, V and Ni+V but not Fe or Ni

5   alone (in saline with the final pH at 3.0) resulted in increased epithelial permeability, decreased

6   cellular glutathione, cell detachment, and lytic cell injury in rat tracheal epithelial cells exposed

7   to soluble salts of these metals at equivalent concentrations found in ROFA (Dye et al., 1999).

8   Treatment of V-exposed cells with buthionine sulfoximine further increased cytotoxicity.

9   Conversely, treatment with radical scavenger dimethyl thiourea inhibited the effects in a dose-

10   dependent manner. These results suggest that soluble metal or combinations of several metals in

11   ROFA may be responsible for these effects.

12   Similar to combustion particles such as ROFA, the biological response to exposure to

13   ambient PM also may be influenced by the metal content of the particles. Human subjects were

14   instilled with 500 μg (in 20 mL sterile saline) of Utah Valley dust (UVD1, 2, 3, collected during

15   3 successive years) on the left segmental bronchus and on the right side with sterile saline as

16   control. Twenty-four-hours post-instillation, a second bronchoscopy was performed and

17   phagocytic cells were obtained on both sides of the segmental bronchus. AM from subjects

18   instilled with UVD, obtained by bronchoaveolar lavage 24 h post-instillation, were incubated

19   with fluoresceinated yeast (Saccharomyces cerevisiae) to assess their phagocytic ability.

20   Although the same proportion of AMs were exposed to UVD phagocytized yeast, AMs exposed

21   to UVD1, which were collected while a local steel mill was open, took up significantly less

22   particles than AMs exposed to other extracts (UVD2 when the steel mill was closed and UVD3

23   when the plant reopened). AMs exposed to UVD1 also exhibited a small decrease in oxidant

24   activity (using dihydrorhodamine-123, DHR). AMs from healthy volunteers were incubated in

25   vitro with the various UVD extracts to assess whether similar effects on human AMs function

26   could be observed to those seen following in vivo exposure. The percentage of AMs that

27   engulfed yeast particles was significantly decreased by exposure to UVD1 at 100 μg/mL, but not

28   at 25 μg/mL. However, the amount of particles engulfed was the same following exposure to all

29   three UVD extracts. AMs also demonstrated increased oxidant stress (using chemiluminescence)

30   after in vitro exposure to UVD1, and this effect was not abolished with pretreatment of the

31   extract with the metal chelator deferoxamine. As with the AMs exposed to UVD in vivo, AM

1   exposed to UVD in vitro had a decreased oxidant activity (DHR assay). UVD1 contains 61 times

2   and 2 times the amount of Zn compared to UVD 2 and UVD3, respectively; whereas UVD3

3   contained 5 times more Fe than UVD1. Ni and V were present only in trace amounts. Using

4   similarly extracted samples, Frampton et al. (1999) exposed BEAS-2B cells for 2 and 24 h.

5   Similar results were observed for oxidant generation in these cells (i.e., UVD 2, which contains

6   the lowest concentrations of soluble iron, copper, and zinc, produced the least response). Only

7   UVD 3 produced cytotoxicity at a dose of 500 μg/mL. UVD 1 and 3, but not 2, induced

8   expression of IL-6 and 8 in a dose-dependent fashion. Taken together, these data showed that the

9   biological response to ambient particle extracts is heavily dependent on the source and; hence,

10   the chemical composition of PM.

11

12   **7.5.3.2 Intracellular Signaling Mechanisms**

13   In has been shown that the intracellular redox state of the cell modulates the activity of

14   several transcription factors, including NF-κB, a critical step in the induction of a variety of

15   proinflammatory cytokine and adhesion-molecule genes. NF-κB is a heterodimeric protein

16   complex that in most cells resides in an inactive state in the cell cytoplasm by binding to

17   inhibitory kappa B alpha (IκBα). On appropriate stimulation by cytokines or ROS, IκBα is

18   phosphorylated and subsequently degraded by proteolysis. The dissociation of IκBα from NF-κB

19   allows the latter to translocate into the nucleus and bind to appropriate sites in the DNA to

20   initiate transcription of various genes. Two studies in vitro have shown the involvement of

21   NF-κB in particulate-induced cytokine and intercellular adhesion molecule-1 (ICAM-1)

22   production in human airway epithelial cells (BEAS-2B) (Quay et al., 1998; Kennedy et al.,

23   1998). Cytokine secretion was preceded by activation of NF-κB and was reduced by treatment

24   with antioxidants or metal chelators. These results suggest that metal-induced oxidative stress

25   may play a significant role in the initiation phase of the inflammatory cascade following

26   particulate exposure.

27   A second well-characterized human transcription factor, AP-1, also responds to the

28   intracellular ROS concentration. AP-1 exists in two forms, either in a homodimer of c-jun

29   protein or a heterodimer consisting of c-jun and c-fos. Small amounts of AP-1 already exist in

30   the cytoplasm in an inactive form, mainly as phosphorylated c-jun homodimer. Many different

31   oxidative stress-inducing stimuli, such as UV light and IL-1, can activate AP-1. Exposure of rat

lung epithelial cells to ambient PM in vitro resulted in increases in c-jun kinase activity, levels of phosphorylated c-jun immunoreactive protein, and transcriptional activation of AP-1-dependent gene expression (Timblin et al., 1998). This study demonstrated that interaction of ambient particles with lung epithelial cells initiates a cell signaling cascade related to aberrant cell proliferation.

Early response gene transactivation has been linked to the development of apoptosis, a unique type of programmed cell injury and a potential mechanism to account for PM-induced changes in cellular response. Apoptosis of human AMs exposed to ROFA (25 μg/mL) or urban PM was observed by Holian et al. (1998). In addition, both ROFA and urban PM upregulated the expression of the RFD1$^+$ AM phenotype; whereas only ROFA decreased the RFD1$^+$7$^+$ phenotype. It has been suggested that an increase in the AM phenotype ratio of RFD1$^+$/RFD1$^+$7$^+$ may be related to disease progression in patients with inflammatory diseases. These data showed that ROFA and urban PM can induce apoptosis of human AMs and increase the ratio of AM phenotypes toward a higher immune active state and may contribute to or exacerbate lung inflammation.

Somatosensory neurons located in the dorsal root ganglia (DRG), innervate the upper thoracic region of the airways and extend their terminals under and between the epithelial lining of the lumen. Given this anatomical proximity, the sensory fibers and their tracheal epithelial targets are the first resident cells to encounter inhaled pollutants, such as PM. The differential response of these cell types to PM derived from various sources (i.e., industrial, residential, volcanic) was examined with biophysical and immunological endpoints (Veronesi et al., 2002a). Although the majority of PM tested stimulated IL-6 release in both BEAS-2B epithelial cells and DRG neurons in a receptor-mediated fashion, the degree of these responses was markedly higher in sensory neurons. Epithelial cells are damaged or denuded in many common health disorders (e.g., asthma, viral infections), allowing PM particles to directly encounter the sensory terminals and their acid sensitive receptors. This differential sensitivity of target cells to PM suggests that non-genetic factors (i.e., cell-cell interactions) may also affect the inflammatory response to PM in individuals whose epithelial lining is damaged.

Another intracellular signaling pathway that can lead to diverse cellular responses such as cell growth, differentiation, proliferation, apoptosis, and stress responses to environmental stimuli, is the phosphorylation-dependent, mitogen-activated protein kinase (MAPK).

1   Noncytotoxic levels of ROFA have been shown to induce significant dose- and time-dependent
2   increases in protein tyrosine phosphate levels in BEAS cells (Samet et al., 1997). In a
3   subsequent study, the effects of As, Cr, Cu, Fe, Ni, V, and Zn on the MAPK, extracellular
4   receptor kinase (ERK), c-jun N-terminal kinase (JNK), and P38 in BEAS cells were investigated
5   (Samet et al., 1998). Noncytotoxic concentrations of As, V, and Zn induced a rapid
6   phosphorylation of MAPK in BEAS cells. Activity assays confirmed marked activation of ERK,
7   JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a
8   relatively small activation of MAPK; whereas Fe and Ni did not activate MAPK. Similarly, the
9   transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly
10   phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn. The same acute exposure to
11   As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein
12   expression in BEAS cells. These data suggest that MAPK may mediate metal-induced
13   expression of inflammatory proteins in human bronchial epithelial cells. The ability of ROFA to
14   induce activation of MAPKs in vivo was demonstrated by Silbajoris et al. (2000) (see Table 7-3).
15   In addition, Gercken et al. (1996) showed that the ROS production induced by PM was markedly
16   decreased by the inhibition of protein kinase C as well as phospholipase A_2.
17   The major cellular response downstream of ROS and the cell signaling pathways described
18   above is the production of inflammatory cytokines or other reactive mediators. In an effort to
19   determine the contribution of cyclooxygenase to the pulmonary responses to ROFA exposure
20   in vivo, Samet et al. (2000) intratracheally instilled Sprague-Dawley rats with ROFA (200 or
21   500 μg in 0.5 mL saline). These animals were pretreated ip with 1 mg/kg NS398, a specific
22   prostaglandin H synthase 2 (COX2) inhibitor, 30 min prior to intratracheal exposure. At 12 h
23   after intratracheal instillations, ip injections (1 mL of NS398 in 20% ethanol in saline) were
24   repeated. ROFA treatment induced a marked increase in the level of PGE_2 recovered in the BAL
25   fluid, which was effectively decreased by pretreating the animals with the COX2 inhibitor.
26   Immunohistochemical analyses of rat airway showed concomitant expression of COX2 in the
27   proximal airway epithelium of rats treated with soluble fraction of ROFA. This study further
28   showed that, although COX2 products participated in ROFA induced lung inflammation, the
29   COX metabolites are not involved in IL-6 expression nor the influx of PMN influx into the
30   airway. However, the rationale for the use of intraperitoneal challenge was not elaborated.

1   The production of cytokines and mediators also has been shown to depend on the type of

2   PM used in the experiments. A549 cells (a human airway epithelial cell line) were exposed to

3   several PM, carbon black (CB, Elftex-12, Cabot Corp.), diesel soot (ND from NIST, LD

4   produced from General Motors LH 6.2 V8 engine at light duty cycle), ROFA (from the heat

5   exchange section of the Boston Edison), OAA (Ottowa ambient air PM, EHC-93), SiO_2, and

6   Ni_3S_2 at 1mg/cm^2 (Seagrave and Nikula, 2000). Results indicated that (1) SiO_2 and Ni_3S_2 caused

7   dose dependent acute toxicity and apototic changes; (2) ROFA and ND were significant only at

8   the highest concentrations; (3) SiO_2 and Ni_3S_2 increased IL-8 (three and eight times over the

9   control, respectively) at low concentrations but suppressed IL-8 at high concentrations; (4) OAA

10   and ROFA also induced IL-8 but lower than SiO_2 and Ni_3S_2; and (5) both diesel soots suppressed

11   IL-8 production. The order of potency in alkaline phasphatase production is OAA > LD =

12   ND > ROFA >> SiO_2 = Ni_3S_2. These results demonstrated that the type of particle used has a

13   strong influence on the biological response.

14   Expression of MIP-2 and IL-6 genes was significantly upregulated as early as 6 h

15   post-ROFA-exposure in rat tracheal epithelial cells; whereas gene expression of iNOS was

16   maximally increased 24 h postexposure. V but not Ni appeared to be mediating the effects of

17   ROFA on gene expression. Treatment with dimethylthiourea inhibited both ROFA and V

18   induced gene expression in a dose-dependent manner (Dye et al., 1999).

19   It appears that many biological responses are produced by PM whether it is composed of a

20   single component or a complex mixture. A technical approach is to use the newly developed

21   gene array to monitor the expressions of many mediator genes, which regulate complex and

22   coordinated cellular events involved in tissue injury and repair, in a single assay. Using an array

23   consisting of 84 rat genes representing inflammatory and anti-inflammatory cytokines, growth

24   factors, adhesion molecules, stress proteins, transcription factors, and antioxidant enzymes,

25   Nadadur et al. (2000) and Nadadur and Kodavanti (2002) measured the pulmonary expressions of

26   these genes in rats intratracheally instilled with ROFA (3.3 mg/kg), $NiSO_4$ (1.3 μmol/kg), and

27   VSO_4 (2.2 μmol/kg). Their data revealed a twofold induction of IL-6 and TIMP-1 at 24 h post-

28   ROFA or Ni exposure. The expression of cellular fibronectin (cFn-EIIIA), ICAM-1, IL-1b, and

29   iNOS gene also were increased 24 h post-ROFA, V, or Ni exposure. This study demonstrated

30   that gene array may provide a tool for screening the expression profile of tissue specific markers

31   following exposure to PM.

1   To investigate the interaction between respiratory cells and PM, Kobzik (1995) showed that

2   scavenger receptors are responsible for AM binding of unopsonized PM and that different

3   mechanisms mediate binding of carbonaceous dusts such as DPM. In addition, surfactant

4   components can increase AM phagocytosis of environmental particulates in vitro, but only

5   slightly relative to the already avid AM uptake of unopsonized particles (Stringer and Kobzik,

6   1996). Respiratory tract epithelial cells are also capable of binding with PM to secrete cytokine

7   IL-8. Using a respiratory epithelial cell line (A549), Stringer et al. (1996) found that binding of

8   particles to epithelial cells was calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding

9   was not calcium dependent. In addition, as observed in AMs, PM binding by A549 cells also

10   was mediated by scavenger receptors, albeit those distinct from the heparin-insensitive

11   acetylated-LDL receptor. Furthermore, α-quartz, but not TiO_2 or CAPs, caused a dose-dependent

12   production of IL-8 (range 1 to 6 ng/mL), demonstrating a particle-specific spectrum of epithelial

13   cell cytokine (IL-8) response.

14

15   **7.5.3.3 Other Potential Cellular and Molecular Mechanisms**

16   A potential mechanism involving in the alteration of surface tension may be related to

17   changes in the expression of matrix metalloproteinases (MMPs), such as pulmonary matrilysin

18   and gelatinase A and B, and tissue inhibitor of metalloproteinase (TIMP) (Su et al., 2000a,b).

19   Sprague-Dawley rats exposed to ROFA by intratracheal injection (2.5 mg/rat) had increased

20   mRNA levels of matrilysin, gelatinase A, and TIMP-1. Gelatinase B, not expressed in control

21   animals, was increased significantly from 6 to 24 h following ROFA exposure. Alveolar

22   macrophages, epithelial cells, and inflammatory cells were major cellular sources for the

23   pulmonary MMP expression. The expression of Gelatinase B in rats exposed to the same dose of

24   ambient PM (<1.7 μm and 1.7 to 3.7 μm) collected from Washington, DC, was significantly

25   increased as compared to saline control; whereas the expression of TIMP-2 was suppressed.

26   Ambient PM between 3.7 and 20 μm also increased the Gelatinase B expression. Increases in

27   MMPs, which degrade most of the extracellular matrix, suggest that ROFA and ambient PM can

28   similarly increase the total pool of proteolytic activity to the lung and contribute in the

29   pathogenesis of PM-induced lung injury.

30   The role of sensory nerve receptors in the initiation of PM inflammation has been described

31   in a series of recent studies. Neuropeptide and acid-sensitive sensory irritant (i.e., capsaicin,

1   VR1) receptors were first identified on human bronchial epithelial cells (i.e., BEAS-2B).

2   To address whether PM could initiate airway inflammation through these acid sensitive sensory

3   receptors, BEAS-2B cells were exposed to ROFA and responded with an immediate increase in

4   $[Ca^{+2}]_i$ followed by a concentration-dependent release of inflammatory cytokine (i.e., IL-6, IL-8,

5   TNFα) and their transcripts (Veronesi et al., 1999a). To test the relevance of neuropeptide or

6   capsaicin VR1 receptors to these changes, BEAS-2B cells were pretreated with neuropeptide

7   receptor antagonists or capsazepine (CPZ), the antagonist for the capsaicin (i.e., VR1) receptor.

8   The neuropeptide receptor antagonists reduced ROFA-stimulated cytokine release by 25%-50%.

9   However, pretreatment of cells with CPZ inhibited the immediate increases in $[Ca^{+2}]_i$, diminished

10 transcript (i.e., IL-6, IL-8, TNFα) levels and reduced IL-6 cytokine release to control levels

11 (Veronesi et al., 1999b). The above studies suggested that ROFA inflammation was mediated by

12 acid sensitive VR1 receptors located on the sensory nerve fibers that innervate the airway and on

13 epithelial target cells.

14   Colloidal particles (like ROFA and other PM) carry an inherently negative surface charge

15 (i.e., zeta potential) that attracts protons from their vaporous milieu. These protons form a

16 neutralizing, positive ionic cloud around the individual particle (Hunter, 1981). Since VR1

17 irritant receptors respond to acidity (i.e., protonic charge), experiments were designed to

18 determine if the surface charge carried by ROFA and other PM particles could biologically

19 activate cells and stimulate inflammatory cytokine release. The mobility of ROFA particles was

20 measured in an electrically charged field (i.e., micro-electrophoresis) microscopically and their

21 zeta potential calculated. Next, synthetic polymer microspheres (SPM) (i.e., polymethacrylic

22 acid nitrophenylacrylate microspheres) were prepared with attached carboxyl groups to yield

23 SPM particles of the same size and with zeta potentials similar to ROFA (-29 + 0.9 mV)

24 particles. These SPM acted as ROFA surrogates with respect to their size and surface charge, but

25 lacked all other contaminants that were thought to be responsible for its toxicity (e.g., transition

26 metals, sulfates, volatile organics and biologicals). Similar concentrations of SPM and ROFA

27 particles were used to test BEAS-2B cells and mouse dorsal root ganglia (DRG) sensory neurons,

28 both targets of inhaled PM. Equivalent degrees of biological activation (i.e., increase in

29 intracellular calcium, $[Ca^{+2}]_i$, IL-6 release) occurred in both cell types in response to either ROFA

30 or SPM and both responses could be reduced by antagonists to VR1 receptors or acid-sensitive

31 pathways. Neutrally charged SPM (i.e., zeta potential of 0 mV), however, failed to stimulated

1 increases in $[Ca^{+2}]_i$ or IL-6 release (Oortgiesen et al., 2000). To expand on these data, a larger set

2 of PM was obtained from urban (St. Louis, Ottawa), residential (wood stove), volcanic (Mt. St.

3 Helen), and industrial (oil fly ash, coal fly ash) sources. Each PM sample was described

4 physicochemically (i.e., size and number of visible particles, acidity, zeta potential) and used to

5 test BEAS-2B epithelial cells. The resulting biological effect (i.e., increases in $[Ca^{+2}]_i$, IL-6

6 release) was related to their physicochemical descriptions. When examined by linear regression

7 analysis, the only measured physicochemical property that correlated with increases in $[Ca^{+2}]_i$ and

8 IL-6 release was the zeta potential of the visible particles ($r^2 > 0.97$) (Veronesi et al., 2002b).

9 Together, these studies have demonstrated a neurogenic basis for PM inflammation by which the

10 proton cloud associated with negatively-charged colloidal PM particles can activate acid-

11 sensitive VR1 receptors found on human airway epithelial cells and sensory terminals. This

12 activation results in an immediate influx of calcium and the release of inflammatory

13 neuropeptides and cytokines which proceed to initiate and sustain inflammatory events in the

14 airways through the pathophysiology of neurogenic inflammation (Veronesi and Oortgiesen,

15 2001).

16

7.5.4 Specific Particle Size and Surface Area Effects

18 Most particles used in laboratory animal toxicology and occupational studies are greater

19 than 0.1 μm in size. However, the enormous number and huge surface area of the ultrafine

20 particles demonstrate the importance of considering the size of the particle in assessing response.

21 Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a

22 number concentration that is approximately 6 orders of magnitude higher than for a 2.5-μm

23 diameter particle; particle surface area is also greatly increased (Table 7-11).

24 Many studies summarized in U.S. Environmental Protection Agency (1996a), as well as in

25 this document, suggest that the surface of particles or substances that are released from the

26 surface (e.g., transition metals) interact with the biological system, and that surface-associated

27 free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine

28 particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the

29 relatively large surface area for a given mass of ultrafine particles would mean high

30 concentrations of transition metals being available to cause oxidative stress to cells.

31

TABLE 7-11. NUMBERS AND SURFACE AREAS OF MONODISPERSE PARTICLES OF UNIT DENSITY OF DIFFERENT SIZES AT A MASS CONCENTRATION OF 10 μg/m^3

Particle Diameter (μm)	Particle Number (per cm^3 air)	Particle Surface Area (μm^2 per cm^3 air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24

Source: Oberdörster (1996).

1   Two groups have examined the toxic differences between fine and ultrafine particles, with

2   the general finding that the ultrafine particles show a significantly greater response at similar

3   mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). However, only a few studies

4   have investigated the ability of ultrafine particles to generate a greater oxidative stress when

5   compared to fine particles of the same material. Studies by Gilmour et al. (1996) have shown

6   that at equal mass, ultrafine TiO_2 caused more plasmid DNA strand breaks than fine TiO_2. This

7   effect could be inhibited with mannitol. Osier and Oberdörster (1997) compared the response of

8   rats (F344) exposed by intratracheal inhalation to "fine" (approximately 250 nm) and "ultrafine"

9   (approximately 21 nm) TiO_2 particles with rats exposed to similar doses by intratracheal

10   instillation. Animals receiving particles through inhalation showed a smaller pulmonary

11   response, measured by BAL parameters, in both severity and persistence, when compared with

12   those animals receiving particles through instillation. These results demonstrate a difference in

13   pulmonary response to an inhaled versus an instilled dose, which may result from differences in

14   dose rate, particle distribution, or altered clearance between the two methods. Consistent with

15   these in vivo studies, Finkelstein et al. (1997) has shown that exposing primary cultures of rat

16   Type II cells to 10 μg/mL ultrafine TiO_2 (20 nm) causes increased TNF and IL-1 release

17   throughout the entire 48-h incubation period. In contrast, fine TiO_2 (200 nm) had no effect.

18   In addition, ultrafine polystyrene carboxylate-modified microspheres (UFP, fluorospheres,

19   molecular probes 44 $\pm$ 5 nm) have been shown to induce a significant enhancement of both

20   substance P and histamine release after administration of capsaicin (10^{-4} M), to stimulate C-fiber,

21   and carbachol (10^{-4} M), a cholinergic agonist in rabbit intratracheally instilled with UFP

1   (Nemmar et al., 1999). A significant increase in histamine release also was recorded in the

2   UFP-instilled group following the administration of both Substance P (10^{-6} M) plus thiorpan

3   (10^{-5} M) and compound 48/80 (C48/80, 10^{-3} M) to stimulate mast cells. BAL analysis showed an

4   influx of PMN, an increase in total protein concentration, and an increase in lung wet weight/dry

5   weight ratio. Electron microscopy showed that both epithelial and endothelial injuries were

6   observed. The pretreatment of rabbits in vivo with a mixture of either SR 140333 and SR 48368,

7   a tachykinin NK_1 and NK_2 receptor antagonist, or a mixture of terfenadine and cimetidine,

8   a histamine H_1 and H_2 receptor antagonist, prevented UFP-induced PMN influx and increased

9   protein and lung WW/DW ratio.

10   Given the assumption that the chemical composition of ultrafine particles is the same as

11   larger particles, it is believed that ultrafine particles cause greater cellular injury because of the

12   relatively large surface area for a given mass. However, in a study that compared the response to

13   carbon black particles of two different sizes, Li et al. (1999) demonstrated that in the instillation

14   model, a localized dose of particle over a certain level causes the particle mass to dominate the

15   response, rather than the surface area. Ultrafine carbon black (ufCB, Printex 90), 14 nm in

16   diameter, and fine carbon black (CB, Huber 990), 260 nm in diameter, were instilled

17   intratracheally in rats and BAL profile at 6 h was assessed. At mass of 125 μg or below, ufCB

18   generated a greater response (increase LDH, epithelial permeability, decrease in GSH, TNF, and

19   NO production) than fine CB at various times postexposure. However, higher dose of CB caused

20   more PMN influx than the ufCB. In contrast to the effect of CB, which showed dose-related

21   increasing inflammatory response, ufCB at the highest dose caused less of a neutrophil influx

22   than at the lower dose, confirming earlier work reported by Oberdörster et al. (1992). Moreover,

23   when the PMN influx was expressed as a function of surface area, CB produced greater response

24   than ufCB at all doses used in this study. Although particle insterstitialization with a consequent

25   change in the chemotatic gradient for PMN was offered as an explanation, these results need

26   further scrutiny.

27   Oberdörster et al. (2000) recently completed a series of studies in rats and mice using

28   ultrafine particles of various chemical compositions (PTFE, TiO_2, C, Fe, Fe_2O_3, Pt, V, and V_2O_5).

29   In old rats sensitized with endotoxin and exposed to ozone plus ultrafine carbon particles, they

30   found a ninefold greater release of reactive oxygen species in old rats than in similarly treated

1   young rats. Exposure to ultrafine PM alone in sensitized old rats also caused an inflammatory

2   response.

3   Although the exact mechanism of ultrafine-induced lung injury remains unclear, it is likely

4   that ultrafine particles, because of their small size, can easily penetrate the airway epithelium and

5   cause cellular damage. Using electron microscopy to examine rat tracheal explants treated with

6   fine (0.12 μm) and ultrafine (0.021 μm) TiO_2 particles for 3 or 7 days, Churg et al. (1998) found

7   both size particles in the epithelium at both time points, but in the subepithelial tissues, they were

8   found only at Day 7. The volume proportion (the volume of TiO_2 over the entire volume of

9   epithelium or subepithelium area) of both fine and ultrafine particles in the epithelium increased

10   from 3 to 7 days. It was greater for ultrafine at 3 days but was greater for fine at 7 days. The

11   volume proportion of particles in the subepithelium at day 7 was equal for both particles, but the

12   ratio of epithelial to subepithelial volume proportion was 2:1 for fine and 1:1 for ultrafine.

13   Ultrafine particles persisted in the tissue as relatively large aggregates; whereas the size of fine

14   particle aggregates became smaller over time. Ultrafine particles appeared to enter the

15   epithelium faster and, once in the epithelium, a greater proportion of them were translocated to

16   the subepithelial space compared to fine particles. However, the authors assumed that the

17   volume proportion is representative of particle number and the number of particles reaching the

18   interstitial space is directly proportional to the number applied (i.e., there is no preferential

19   transport from lumen to interstitium by size). These data are in contrast to the results of

20   instillation or inhalation of fine and ultrafine TIO_2 particles reported earlier (Ferin et al., 1990,

21   1992). However, the explant and intratracheal instillation test systems differ in many aspects

22   making direct comparisons difficult. Limitations of the explant test system include traumatizing

23   the explanted tissue, introducing potential artifacts through the use of liquid suspension for

24   exposure, the absence of inflammatory cells, and possible overloading of the explants with dust.

25   Only two studies examined the influence of specific surface area on biological activity

26   (Lison et al., 1997; Oettinger et al., 1999). The biological responses to various MnO_2 dusts with

27   different specific surface area (0.16, 0.5, 17, and 62 m^2/g) were compared in vitro and in vivo

28   (Lison et al., 1997). In both systems, the results show that the amplitude of the response is

29   dependent on the total surface area that is in contact with the biological system, indicating that

30   surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles

31   with a specific surface area of 5 m^2/g also were examined in vitro. These particles exhibited an

1   enhanced cytotoxic activity that was almost equivalent to that of particles with a specific surface

2   area of 62 m^2/g, indicating that undefined reactive sites produced at the particle surface by

3   mechanical cleavage also may contribute to the toxicity of insoluble particles. In another study,

4   two types of carbon black particles, Printex 90 (P90, Degussa, Germany, formed by controlled

5   combustion, consists of defined granules with specific surface area of 300 m^2/g and particle size

6   of 14 nm) and FR 101 (Degussa, Germany, with specific surface area of 20 m^2/g and particle size

7   of <95 nm, has a coarse structure, and the ability to adsorb polycyclic and other carbons) were

8   used in the study (Oettinger et al., 1999). Exposure of AMs to 100 μg/10^6 cells of FR 101 and

9   P90 resulted in a 1.4- and 2.1-fold increase in ROS release. These exposures also caused a

10   fourfold up-regulation of NF-κB gene expression. These studies indicated that PM of single

11   component with larger surface area produce greater biological response than similar particles

12   with smaller surface area. By exposing bovine AMs to metal oxide coated silica particles,

13   Schluter et al. (1995) showed that most of the metal coatings (As, Ce, Fe, Mn, Ni, Pb, and V) had

14   no effect on ROS production by these cells. However, coating with CuO markedly lowered the

15   O$_2^-$ and H$_2$O$_2$, whereas V(IV) increases both ROI. This study demonstrated that, in addition to

16   specific area, chemical composition of the particle surface also influence its cellular response.

17   Thus, ultrafine particles have the potential to significantly contribute to the adverse effects of

18   PM. These studies, however, have overlooked the portion of ambient ultrafine particles that are

19   not solid in form. Droplets (e.g., sulfuric acid droplets) and organic based ultrafine particles do

20   exist in the ambient environment, but their role in the adverse effects of ultrafine particles has

21   been ignored. Moreover, the ability of these droplet ultrafine particles to spread, disperse, or

22   dissolve after contact with liquid surface layers must be considered.

23

24   ## 7.5.5 Pathophysiological Mechanisms for the Effects of Low Concentrations
25   of Particulate Air Pollution

26   The pathophysiological mechanisms involved in PM-associated cardiovascular and

27   respiratory health effects still are not elucidated fully, but progress has been made since the 1996

28   PM AQCD (U. S. Environmental Protection Agency, 1996a) was prepared. This section

29   summarizes several current hypotheses and reviews the toxicological evidence for these potential

30   pathophysiological mechanisms.

31

1   **7.5.5.1 Direct Pulmonary Effects**

2   When the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a) was written,

3   the lung was thought to be the primary organ that was affected by particulate air pollution.

4   Although the lung still is a primary organ affected by PM inhalation, there is growing

5   toxicological and epidemiological evidence that the cardiovascular system is affected, as well,

6   and may be a co-primary organ system related to certain health endpoints such as mortality.

7   Nonetheless, understanding how particulate air pollution causes or exacerbates respiratory

8   disease remains an important goal. There is some toxicological evidence for the following three

9   mechanisms for direct pulmonary effects.

10

11   *Particulate Air Pollution Causes Lung Injury and Inflammation*

12   In the last few years, numerous studies have shown that instilled and inhaled ROFA, a

13   product of fossil fuel combustion, can cause substantial lung injury and inflammation. The toxic

14   effects of ROFA are largely caused by its high content of soluble metals, and some of the

15   pulmonary effects of ROFA can be reproduced by equivalent exposures to soluble metal salts.

16   In contrast, controlled exposures of animals to sulfuric acid aerosols, acid-coated carbon, and

17   sulfate salts cause little lung injury or inflammation, even at high concentrations. Inhalation of

18   concentrated ambient PM (which contains only small amounts of metals) by laboratory animals

19   at concentrations in the range of 100 to 1000 μg/m^3 have been shown in some (but not all)

20   studies to cause mild pulmonary injury and inflammation. Rats with SO_2-induced bronchitis and

21   monocrotaline-treated rats have been reported to have a greater inflammatory response to

22   concentrated ambient PM than normal rats. These studies suggest that exacerbation of

23   respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

24

25   *Particulate Air Pollution Causes Increased Susceptibility to Respiratory Infections*

26   At this time there are no newly published studies on the effects of inhaled concentrated

27   ambient PM on host susceptibility to infectious agents. Ohtsuka et al. (2000a,b) have shown that

28   in vivo exposure of mice to acid-coated carbon particles at a mass concentration of 10,000 μg/m^3

29   carbon black causes decreased phagocytic activity of alveolar macrophages, even in the absence

30   of lung injury.

31

1   *Particulate Air Pollution Increases Airway Reactivity and Exacerbates Asthma*

2   The strongest evidence supporting this hypothesis is from studies on diesel particulate

3   matter (DPM). DPM has been shown to increase production of antigen-specific IgE in mice and

4   humans (summarized in Section 7.2.1.2). In vitro studies have suggested that the organic

5   fraction of DPM is involved in the increased IgE production. ROFA leachate also has been

6   shown to enhance antigen-specific airway reactivity in mice (Goldsmith et al., 1999), indicating

7   that soluble metals can also enhance an allergic response. However, in this same study, exposure

8   of mice to concentrated ambient PM did not affect antigen-specific airway reactivity. It is

9   premature to conclude from this one experiment that concentrated ambient PM does not

10   exacerbate allergic airways disease because the chemical composition of the PM (as indicated by

11   studies with DPM and ROFA) may be more important than the mass concentration.

12

13   **7.5.5.2 Systemic Effects Secondary to Lung Injury**

14   When the 1996 PM AQCD was written, it was thought that cardiovascular-related

15   morbidity and mortality most likely would be secondary to impairment of oxygenation or some

16   other consequence of lung injury and inflammation. Newly available toxicologic studies provide

17   some additional evidence regarding such possibilities.

18

19   *Lung Injury from Inhaled Particulate Matter Causes Impairment of Oxygenation and*
20   *Increased Work of Breathing That Adversely Affects the Heart*

21
22   Instillation of ROFA has been shown to cause a 50% mortality rate in monocrotaline-

23   treated rats (Watkinson et al., 2000a,b). Although blood oxygen levels were not measured in this

24   study, there were ECG abnormalities consistent with severe hypoxemia in about half of the rats

25   that subsequently died. Given the severe inflammatory effects of instilled ROFA and the fact

26   that monocrotaline-treated rats have increased lung permeability as well as pulmonary

27   hypertension, it is plausible that instilled ROFA can cause severe hypoxemia leading to death in

28   this rat model. Results from studies in which animals (normal and compromised) were exposed

29   to concentrated ambient PM (at concentrations many times higher than would be encountered in

30   the United States) indicate that ambient PM is unlikely to cause severe disturbances in

31   oxygenation or pulmonary function. However, even a modest decrease in oxygenation can have

32   serious consequences in individuals with ischemic heart disease. Kleinman et al. (1998) has

1   shown that a reduction in arterial blood saturation from 98 to 94% by either mild hypoxia or by

2   exposure to 100 ppm CO significantly reduced the time to onset of angina in exercising

3   volunteers. Thus, information is needed on the effects of PM on arterial blood gases and

4   pulmonary function to fully address the above hypothesis.

5

6   *Lung Inflammation and Cytokine Production Cause Adverse Systemic Hemodynamic Effects*

7   It has been suggested that systemic effects of particulate air pollution may result from

8   activation of cytokine production in the lung (Li et al., 1997). In support of this idea,

9   monocrotaline-treated rats exposed to inhaled ROFA (15,000 μg/m^3, 6 h/day for 3 days) showed

10 increased pulmonary cytokine gene expression, bradycardia, hypothermia, and increased

11 arrhythmias (Watkinson et al., 2000a,b). However, spontaneously hypertensive rats had a similar

12 cardiovascular response to inhaled ROFA (except that they also developed ST segment

13 depression) with no increase in pulmonary cytokine gene expression. Studies in dogs exposed to

14 concentrated ambient PM showed minimal pulmonary inflammation and no positive staining for

15 IL-8, IL-1, or TNF in airway biopsies. However, there was a significant decrease in the time of

16 onset of ischemic ECG changes following coronary artery occlusion in PM-exposed dogs

17 compared to controls (Godleski et al., 2000). Thus, the link between changes in the production

18 of cytokines in the lung and cardiovascular function is not clear-cut, and basic information on the

19 effects of mild pulmonary injury on cardiovascular function is needed to understand the

20 mechanisms by which inhaled PM affects the heart.

21

22 *Lung Inflammation from Inhaled Particulate Matter Causes Increased Blood Coagulability*
23 *That Increases the Risk of Heart Attacks and Strokes*
24
25   There is abundant evidence linking risk of heart attacks and strokes to small prothrombotic

26 changes in the blood coagulation system. However, the published toxicological evidence that

27 moderate lung inflammation causes increased blood coagulability is inconsistent. Ghio et al.

28 (2000a) have shown that inhalation of concentrated ambient PM in healthy nonsmokers causes

29 increased levels of blood fibrinogen. Gardner et al. (2000) have shown that a high dose

30 (8,300 μg/kg) of instilled ROFA in rats causes increased levels of fibrinogen, but no effect was

31 seen at lower doses. Exposure of dogs to concentrated ambient PM had no effect on fibrinogen

32 levels (Godleski et al., 2000). The coagulation system is as multifaceted and complex as the

1   immune system, and there are many other sensitive and clinically significant parameters that

2   should be examined in addition to fibrinogen. Thus, it is premature to draw any conclusions on

3   the relationship between PM and blood coagulation.

4

5   *Interaction of Particulate Matter with the Lung Affects Hematopoiesis*

6   Terashima et al. (1997) found that instillation of fine carbon particles (20,000 μg/rabbit)

7   stimulated release of PMNs from the bone marrow. In further support of this hypothesis, Gordon

8   and colleagues reported that the percentage of PMNs in the peripheral blood increased in rats

9   exposed to ambient PM in some but not all exposures. On the other hand, Godleski et al. (2000)

10   found no changes in peripheral blood counts of dogs exposed to concentrated ambient PM.

11   Thus, direct evidence that PM ambient concentrations can affect hematopoiesis remains to be

12   demonstrated.

13

14   **7.5.5.3 Direct Effects on the Heart**

15   Changes in heart rate, heart rate variability, and conductance associated with ambient PM

16   exposure have been reported in animal studies (Godleski et al., 2000; Gordon et al., 2000;

17   Watkinson et al., 2000a,b; Campen et al., 2000), in several human panel studies (described in

18   Chapter 8), and in a reanalysis of data from the MONICA study (Peters et al., 1997). Some of

19   these studies included endpoints related to respiratory effects but few significant adverse

20   respiratory changes were detected. This raises the possibility that ambient PM may have effects

21   on the heart that are independent of adverse changes in the lung. There is certainly precedent for

22   this idea. For example, tobacco smoke (which is a mixture of combustion-generated gases and

23   PM) causes cardiovascular disease by mechanisms that are independent of its effect on the lung.

24   Two types of hypothesized direct effects of PM on the heart are noted below.

25

26   *Inhaled Particulate Matter Affects the Heart by Uptake of Particles into the Circulation*
27   *or Release of a Soluble Substances into the Circulation.*
28
29   Drugs can be rapidly and efficiently delivered to the systemic circulation by inhalation.

30   This implies that the pulmonary vasculature absorbs inhaled materials, including charged

31   substances such as small proteins and peptides. Cigarettes are a widely used method for

32   delivering nicotine to the blood stream. It is likely that soluble materials absorbed onto airborne

1 particles find their way into the blood stream, but it is not clear whether the particles themselves

2 enter the blood. It is anticipated that more information will be available on this important

3 question in the next few years.

4

5 *Inhaled Particulate Matter Affects Autonomic Control of the Heart and*
6 *Cardiovascular System*

7
8 There is growing evidence for this idea as described above. This raises the question of how

9 inhaled particles could affect the autonomic nervous system. Activation of neural receptors in

10 the lung is a logical area to investigate. Studies in conscious rats have shown that inhalation of

11 wood smoke causes marked changes in sympathetic and parasympathetic input to the

12 cardiovascular system that are mediated by neural reflexes (Nakamura and Hayashida, 1992).

13 Although research on airway neural receptors and neural-mediated reflexes is a well established

14 discipline, the cardiovascular effects of stimulating airway receptors continue to receive less

15 attention than the pulmonary effects. Previous studies of airway reflex-mediated cardiac effects

16 usually employed very high doses of chemical irritants, and the results may not be applicable to

17 air pollutants. There is a need for basic physiological studies to examine effects on

18 cardiovascular system when airway and alveolar neural receptors are stimulated in a manner

19 relevant to air pollutants.

20

21

22 ## 7.6 RESPONSES TO PARTICULATE MATTER AND GASEOUS
23 POLLUTANT MIXTURES

24 Ambient PM itself is a mixture of particles of varying size and composition. The following

25 discussion examines effects of mixtures of ambient PM, or PM surrogates, with gaseous

26 pollutants. Ambient PM co-exists in indoor and outdoor air with a number of co-pollutant gases,

27 including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide. Toxicological

28 interactions between PM and gaseous co-pollutants may be antagonistic, additive, or synergistic

29 (Mauderly, 1993). The presence and nature of any interaction appears to depend on the chemcial

30 composition, size, concentration and ratios of pollutants in the mixture, exposure duration, and

31 the endpoint being examined. It may be difficult to predict a priori from the presence of certain

1   pollutants whether any interaction will occur and, if there is interaction, whether it will be

2   synergistic, additive, or antagonistic (Table 7-12).

3   Mechanisms responsible for the various forms of interaction are speculative. In terms of

4   potential health effects, the greatest hazard from pollutant interaction is the possibility of synergy

5   between particles and gases, especially if effects occur at concentrations at which no effects

6   occur when individual constituents are inhaled. Various physical and chemical mechanisms may

7   underlie synergism. For example, physical adsorption or absorption of some material on a

8   particle could result in transport to more sensitive sites, or sites where this material would not

9   normally be deposited in toxic amounts. This physical process may explain the interaction found

10   in studies of mixtures of carbon black and formaldehyde or of carbon black and acrolein (Jakab,

11   1992, 1993).

12   Chemical interactions between PM and gases can occur on particle surfaces, thus, forming

13   secondary products that may be more active toxicologically than the primary materials and that

14   can then be carried to a sensitive site. The hypothesis of such chemical interactions has been

15   examined in the gas and particle exposure studies by Amdur and colleagues (Amdur and Chen,

16   1989; Chen et al., 1992) and Jakab and colleagues (Jakab and Hemenway, 1993; Jakab et al.,

17   1996). These investigators have suggested that synergism occurs as secondary chemical species

18   are produced, especially under conditions of increased temperature and relative humidity.

19   Another potential mechanism of gas-particle interaction may involve a pollutant-induced

20   change in the local microenvironment of the lung, enhancing the effects of the co-pollutant.

21   For example, Last et al. (1984) suggested that the observed synergism between ozone (O_3) and

22   acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung

23   following deposition of acid, enhancing the effects of O_3 by producing a change in the reactivity

24   or residence time of reactants, such as radicals, involved in O_3-induced tissue injury. Likewise,

25   Pinkerton et al (1989) showed increased retention of the mass and number of asbestos fibers in

26   rats exposed to O_3, suggesting an increase in lung fiber burden due to exposure to this gaseous

27   pollutant.

28   As noted in U.S. Environmental Protection Agency (1996a), the toxicology database for

29   mixtures containing PM other than acid sulfates was and is still quite sparse. Vincent et al.

30   (1997) exposed rats to 0.8 ppm O_3 in combination with 5 or 50 mg/m^3 of resuspended urban

31   particles for 4 h. Although PM alone caused no change in cell proliferation (^{3}H-thymidine

TABLE 7-12. RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Rats, Fischer NNia, male, 22 to 24 mo old	Carbon, ammonium bisulfate, and O_3	Inhalation	50 μg/m³ carbon + 70 μg/m³ ammonium bisulfate + 0.2 ppm O_3 or 100 μg/m³ carbon +140 μg/m³ ammonium bisulfate + 0.2 ppm O_3	0.4 μm MMAD σg = 2.0	4 h/day, 3 days/week for 4 weeks	No changes in protein concentration in lavage fluid or in prolyl 4-hydroxylase activity in blood. Slight, but statistically significant decreases in plasma fibronectin in animals exposed to the combined atmospheres compared to animals exposed to O_3 alone.	Bolarin et al. (1997)
Rats	O_3 and Ottawa urban dust	Inhalation	40,000 μg/m³ and 0.8 ppm O_3	4.5 μm MMAD	Single 4-h exposure followed by 20 h clean air	Co-exposure to particles potentiated O_3-induced septal cellurity. Enhanced septal thickening associated with elevated production of macrophage inflammatory protein-2 and endothelin 1 by lung lavage cells.	Bouthillier et al. (1998)
Humans; healthy 15 M, 10 F, 34.9±10 years of age	CAPs	Inhalation	150 μg/m³ 120 ppb	PM$_{2.5}$ O_3	2 h	Acute brachial artery vasoconstriction as determined by vascular ultrasonography performed before and 10 min after exposure.	Brook et al. (2002)
Humans; healthy children	Ambient gases and particles	Natural 24 h exposure in Southwest Metropolitan Mexico City (SWMMC)				Radiological evidence of lung hyperinflation from chest X-rays.	Calderón-Garcidueñas et al. (2000a)
Humans; 59 healthy childern in Mexico City; 19 controls in Gulf port town	Ambient gases and particles	Natural 24 h exposure in SWMMC compared to low pollution Gulf of Mexico				Increased upper and lower respiratory symptoms; bilateral symmetric mild lung hyperinflation from chest X-rays.	Calderón-Garcidueñas et al. (2000b)
Humans; 15 healthy children in Mexico City; 11 children in Veracruz; 4-15 years of age	Ambient gases and particles	Natural 24 h exposure in SWMMC compared to low pollution Gulf Coast				Nasal biopsies revealed increased basal, ciliated, goblet, and squamous metaplastic and intermediate cells; cellular abnormalities and possible dyskinesia were noted.	Calderón-Garcidueñas et al. (2001a)
Humans; 83 healthy children in Mexico City; 24 children in Isla Mujeres; 6-12 years of age	Ambient gases and particles	Natural 24 h exposure in SWMMC compared to low pollution Caribbean				Nasal biopsies revealed p53 accumulation by immunochemistry; increased upper and lower respiratory symptoms.	Calderón-Garcidueñas et al. (2001b)

TABLE 7-12 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Dogs, 109 healthy male and female mongrels form Mexico City; 43 dogs from less-polluted cities	Ambient gases and particles	Natural 24 h exposure in SWMMC and NWMMC compared to low pollution cities				LM and EM of lungs exhibited patchy chronic mononuclear cell infiltrates and AMs loaded with particles; bronchiolar and smooth muscle hyperplasia; peribronchiolar fibrosis; BAL demonstrated proliferating AMs.	Calderón-Garcidueñas et al. (2001c)
						LM and EM of heart exhibited increased myocardial abnormalities and including apototic myocytes, endothelial and immune effector cells, degramulated mast cells, and clusters of adipocytes.	Calderón-Garcidueñas et al. (2001d)
Mice, Swiss, female, 5 weeks old	SO_2 and carbon	Inhalation, flow-past, nose-only	$10,000\ \mu g/m^3$ carbon with or without 5 to 20 ppm SO_2 at 10% or 85% RH	$0.3\ \mu m$ MMAD $\sigma g = 2.7$	Single 4-h exposure	Macrophage phagocytosis was depressed only in animals exposed to the combination of SO_2 and carbon at 85% humidity. This inhibition in macrophage function lasted at least 7 days after exposure.	Jakab et al. (1996)
Rats, S-D, male, 250-300 g	H_2SO_4 and O_3	Inhalation, nose-only	$500\ \mu g/m^3$ H_2SO_4 aerosol (two different particle sizes), with or without 0.6 ppm O_3	Fine ($0.3\ \mu m$ MMD, $\sigma g = 1.7$) and ultrafine ($0.06\ \mu m$, $\sigma g = 1.4$)	4 h/day for 2 days	The volume percentage of injured alveolar septae was increased only in the combined ultrafine acid/O_3 animals. BrdU labeling in the periacinar region was increased in a synergistic manner in the combined fine acid/O_3 animals.	Kimmel et al. (1997)
Rats, S-D 300 g	O_3 and H_2SO_4-coated carbon	Inhalation, nose-only	0.2 ppm O_3 + $50\ \mu g/m^3$ C + $100\ \mu g/m^3$ H_2SO_4 0.4 ppm O_3 + $250\ \mu g/m^3$ C + $500\ \mu g/m^3$ H_2SO_4	$0.26\ \mu m$ $\sigma g = 2.2$	4 h/day for 1 day or 5 days	No airway inflammation at low dose. Greater inflammatory response at high dose; greater response at 5 days than 1 day. Contrasts with O_3 alone where inflammation was greatest at 0.40 ppm on Day 1.	Kleinman et al. (1999)
Rats	O_3 + elemental carbon + ammonium bisulfate	Inhalation	0.2 ppm O_3 + carbon $50\ \mu m/m^3$ ammonium Bisulfate $70\ \mu g/m^3$	$0.46\ \mu m$ $0.3\ \mu m$	4 hr/d 3 d/wk 4 wk	Increased macrophage phagocytosis and increased respiratory burst; decreased lung collagen	Kleinman et al. (2000)
Mice, BALB/c, 3 days old	CAPs (Boston) O_3	Inhalation	$63-1569\ \mu g/m^3$ 0.3 ppm	$PM_{2.5}$	5 h	A small increase in pulmonary resistance and airway responsiveness was found in both normal mice and mice with ovalbumin-induced asthma immediately after exposure to CAPs, but not O_3; no evidence of synergy; activity attributed to the AlSi PM component	Kobzik et al. (2001)

TABLE 7-12 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Rats	H_2SO_4 and O_3	Inhalation, whole body	20 to 150 $\mu g/m^3$ H_2SO_4 and 0.12 or 0.2 ppm O_3	0.4 to 0.8 μm	Intermittent (12 h/day) or continuous exposure for up to 90 days	No interactive effect of H_2SO_4 and O_3 on biochemical and morphometric endpoints.	Last and Pinkerton (1997)
Humans, children, healthy and asthmatic	H_2SO_4, SO_2, and O_3	Inhalation	60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3	0.6 μm H_2SO_4	Single 4-h exposure with intermittent exercise	A positive association between acid concentration and symptoms, but not spirometry, in asthmatic children. No changes in healthy children.	Linn et al. (1997)
Pigeons (Columba livia)	Ambient gases and particles	Natural 24-h exposure in urban and rural areas around Madrid, Spain			Continuous ambient exposure	Increased number of AMs and decreased number of lamellar bodies in type II epithelial cells in urban pigeons.	Lorz and López (1997)
Rats, F344/N male	O_3 + nitric acid NO_2 + carbon particles + ammonium bisulfate	Inhalation			4 h/d 3 d/wk 4 wk	Decreases in macrophage Fc-receptor mediated-phagocytosis, increased epithelial permeability and proliferation, altered breathing pattern.	Mautz et al. (2001)
Rats, F344, 9-weeks-old, male and female	Ambient gases and particles	Natural 23 h/day exposure to filtered and unfiltered Mexico City air.	0.018 ppm O_3 3.3 ppb CH_2O 0.068 mg/m^3 TSP 0.032 mg/m^3 PM_{10} 0.016 mg/m^3 $PM_{2.5}$		23 h/day for 7 weeks	Histopathology examination revealed no nasal lesions in exposed or control rats; tracheal and lung tissue from both groups showed similar levels of minor abnormalities.	Moss et al. (2001)
Rats, F344/N male	O_3 + nitric acid NO_2 + carbon particles + ammonium bisulfate	Inhalation			4 h/d 3 d/wk 40 wk	Increased lung putrescine content.	Sindhu et al. (1998)
Dogs	Ambient gases and particles	Natural 24-h exposure in four urban areas of Mexico City and one rural area			Continuous ambient exposure	No significant differences in AMs or total cell counts in lavage from dogs studied among the five regions. A significant increase in lavage fluid neutrophils and lymphocytes in the southwest region, where the highest O_3 levels were recorded, compared to the two industrial regions with the highest PM levels.	Vanda et al. (1998)
Rats	O_3 and resuspended urban PM	Inhalation, whole-body	0.8 ppm O_3 and 5,000 or 50,000 $\mu g/m^3$ PM		Single 4-h exposure	PM alone caused no change in cell proliferation in bronchioles or parenchyma. Co-exposure with O_3 greatly potentiated the proliferative changes induced by O_3 alone. These changes were greatest in the epithelium of the terminal bronchioles and alveolar ducts.	Vincent et al. (1997)

labeling), co-exposure to either concentration of resuspended PM with O_3 greatly potentiated the proliferative effects of exposure to O_3 alone. These interactive changes occurred in epithelial cells of the terminal bronchioles and the alveolar ducts. These findings using resuspended dusts, although at high concentrations, are consistent with studies demonstrating interaction between sulfuric acid (H_2SO_4) aerosols and O_3. Kimmel and colleagues (1997) examined the effect of acute co-exposure to O_3 and fine or ultrafine H_2SO_4 aerosols on rat lung morphology. They determined morphometrically that alveolar septal volume was increased in animals co-exposed to O_3 and ultrafine, but not fine, H_2SO_4. Interestingly, cell labeling, an index of proliferative cell changes, was increased only in animals co-exposed to fine H_2SO_4 and O_3, as compared to animals exposed to O_3 alone. Importantly, Last and Pinkerton (1997) extended their previous work and found that subchronic exposure to acid aerosols (20 to 150 $\mu g/m^3$ H_2SO_4) had no interactive effect on the biochemical and morphometric changes produced by either intermittent or continuous O_3 exposure (0.12 to 0.2 ppm). Thus, the interactive effects of O_3 and acid aerosol co-exposure in the lung disappeared during the long-term exposure. Sindhu et al. (1998) observed an increase in rat lung putrescine levels after repeated, combined exposures to O_3 and a nitric acid vapor.

Kleinman et al. (1999) examined the effects of O_3 plus fine, H_2SO_4-coated, carbon particles (MMAD = 0.26 μm) for 1 or 5 days. They found the inflammatory response with the O_3-particle mixture was greater after 5 days (4 h/day) than after Day 1. This contrasted with O_3 exposure alone (0.4 ppm), which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure.

Kleinman et al. (2000) examined the effects of a mixture of elemental carbon particles, O_3, and ammonium bisulfate on rat lung collagen content and macrophage activity. Decreases in lung collagen, and increases in macrophage respiratory burst and phagocytosis were observed relative to other pollutant combinations. Mautz et al. (2001) used a similar mixture (i.e., elemental carbon particles, O_3, ammonium bisulfate, but with NO_2 also) and exposure regimen as Kleinman (2000). There were decreases in pulmonary macrophage Fc-receptor binding and phagocytosis and increases in acid phosphatase staining. Bronchoalveolar epithelial permeability cell proliferation were increased. Altered breathing-patterns were also observed, with some adaptations occurring.

1   Studies have examined interactions between carbon particles and gaseous co-pollutants.

2   Jakab et al. (1996) challenged mice with a single 4-h exposure to a high concentration of carbon

3   particles (10 mg/m^3) in the presence of SO_2 at low and high relative humidities. Macrophage

4   phagocytosis was depressed significantly only in mice exposed to the combined pollutants under

5   high relative humidity conditions. This study suggests that fine carbon particles can serve as an

6   effective carrier for acidic sulfates where chemical conversion of adsorbed SO_2 to acid sulfate

7   species occurred. Interestingly, the depression in macrophage function was present as late as

8   7 days postexposure. Bolarin et al. (1997) exposed rats to only 50 or 100 $\mu g/m^3$ carbon particles

9   in combination with ammonium bisulfate and O_3. Despite 4 weeks of exposure, they observed

10   no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme

11   involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals

12   exposed to the combined pollutants versus O_3 alone. Thus as, previously noted, the potential for

13   adverse effects in the lungs of animals challenged with a combined exposure to particles and

14   gaseous pollutants is dependent on numerous factors, including the gaseous co-pollutant,

15   concentration, and time.

16   In a complex series of exposures, Oberdörster and colleagues examined the interaction of

17   ultrafine carbon particles (100 $\mu g/m^3$) and O_3 (1 ppm) in young and old Fischer 344 rats that were

18   pretreated with aerosolized endotoxin (Elder et al., 2000a,b). In old rats, exposure to carbon and

19   O_3 produced an interaction that resulted in a greater influx in neutrophils than that produced by

20   either agent alone. This interaction was not seen in young rats. Oxidant release from lavage

21   fluid cells was also assessed and the combination of endotoxin, carbon particles, and O_3

22   produced an increase in oxidant release in old rats. This combination produced the opposite

23   response in the cells recovered from the lungs of the young rats, indicating that the lungs of the

24   aged animals underwent greater oxidative stress in response to this complex pollutant mix of

25   particles, O_3, and a biogenic agent.

26   Wagner et al. (2001) examined the synergistic effect of co-exposure to O_3 and endotoxin on

27   the transition and respiratory epithelium of rats that also was mediated, in part, by neutrophils.

28   Fisher 344 rats (10 to 12 week old) exposed to 0.5 ppm O_3, 8 h per day, for 3 days, developed

29   mucous cell metaplasia in the nasal transitional epithelium, an area normally devoid of mucous

30   cells; whereas, intratracheal instillation of endotoxin (20 μg) caused mucous cell metaplasia

31   rapidly in the respiratory epithelium of the conducting airways. A synergistic increase of

1   intraepithelial mucosubstances and morphological evidence of mucous cell metaplasia were

2   found in rat maxilloturbinates upon exposure to both ozone and endotoxin, compared to each

3   pollutant alone.

4   The effects of O_3 modifying the biological potency of PM (diesel PM and carbon black)

5   was examined by Madden et al. (2000). Reaction of NIST Standard Reference Material # 2975

6   diesel PM with 0.1 ppm O_3 for 48 hr increased the potency (compared to unexposed or

7   air-exposed diesel PM) to induce neutrophil influx, total protein, and LDH in lung lavage fluid in

8   response to intratracheal instillation. Exposure of the diesel PM to high, non-ambient O_3

9   concentration (1.0 ppm) attenuated the increased potency, suggestion destruction of the bioactive

10   reaction products. Unlike the diesel particles, carbon black particles exposed to 0.1 ppm O_3 did

11   not exhibit an increase in biological potency, which suggested that the reaction of organic

12   components of the diesel PM with O_3 were responsible for the increased potency. Reaction of

13   particle components with O_3 was ascertained by chemical determination of specific classes of

14   organic compounds.

15   The interaction of PM and O_3 was further examined in a murine model of ovalbumin

16   (OVA)-induced asthma. Kobzik et al. (2001) investigated whether coexposure to inhaled,

17   concentrated PM from Boston, MA and to O_3 could exacerbate asthma-like symptoms. On days

18   7 and 14 of life, half of the BALB/c mice used in this study were sensitized by ip injection of

19   OVA and then exposed to OVA aerosol on three successive days to create the asthma phenotype.

20   The other half received the ip OVA, but were exposed to a phosphate-buffered saline aerosol

21   (controls). The mice were further subdivided (n $\geq$61/group) and exposed for 5 h to CAPs,

22   ranging from 63 to 1,569 μg/m^3, 0.3 ppm O_3, CAPs + O_3, or to filtered air. Pulmonary resistance

23   and airway responsiveness to an aerosolized MCh challenge were measured after exposures. A

24   small, statistically significant increase in pulmonary resistance and airway responsiveness,

25   respectively, was found in both normal and asthmatic mice immediately after exposure to CAPs

26   alone and to CAPs + O_3, but not to O_3 alone or to filtered air. By 24 h after exposure, the

27   responses returned to baseline levels. There were no significant increases in airway

28   inflammation after any of the pollutant exposures. In this well-designed study of a small-animal

29   model of asthma, O_3 and CAPs did not appear to be synergistic. In further analysis of the data

30   using specific elemental groupings of the CAPs, the acutely increased pulmonary resistance was

31   found to be associated withe the AlSi fraction of PM. Thus, some components of concentrated

1   PM$_{2.5}$ may affect airway caliber in sensitized animals, but the results are difficult to extrapolate to

2   people with asthma.

3   Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 μg/m^3

4   H$_2$SO$_4$, 0.1 ppm SO$_2$, and 0.1 ppm O$_3$ in healthy and asthmatic children. The children performed

5   intermittent exercise during the 4-h exposure to increase the inhaled dose of the pollutants. An

6   overall effect on the combined group of healthy and asthmatic children was not observed. A

7   positive association between acid concentration and symptoms was seen, however, in the

8   subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in

9   asthmatic children, and no changes in symptoms or spirometry were observed in healthy children.

10 Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less

11 effect on asthmatic children exposed under controlled laboratory conditions in comparison with

12 field studies of children attending summer camp (Thurston et al., 1997). However, prior

13 exposure to H$_2$SO$_4$ aerosol may enhance the subsequent response to O$_3$ exposure (Linn et al.,

14 1994; Frampton et al., 1995); and the timing and sequence of the exposures may be important.

15   Six unique animal studies have examined the adverse cardiopulmonary effects of complex

16 mixtures in urban and rural environments of Italy (Gulisano et al., 1997), Spain (Lorz and Lopez,

17 1997), and Mexico (Vanda et al., 1998; Calderón-Garcidueñas et al., 2001c,d; Moss et al., 2001).

18 Five of these studies, identified in Table 7-12, have taken advantage of the differences in

19 pollutant mixtures of urban and rural environments to report primarily morphological changes in

20 the nasopharynx and lower respiratory tract (Gulisano et al., 1997; Lorz and Lopez, 1997;

21 Calderón-Garcidueñas et al., 2001c) and in the heart (Calderón-Garcidueñas et al., 2001d) of

22 lambs, pigeons, and dogs, respectively, after natural, continuous exposures to ambient pollution.

23 Each study has provided evidence that animals living in urban air pollutants have greater

24 pulmonary and cardiac changes than would occur in a rural and presumably cleaner,

25 environment. The study by Moss et al. (2001) examined the nasal and lung tissue of rats exposed

26 (23 h/day) to Mexico City air for up to 7 weeks and compared them to controls similarly exposed

27 to filtered air. No inflammatory or epithelial lesions were found using quantitative

28 morphological techniques; however, the concentrations of pollutants were low (see Table 7-12).

29 Extrapolation of these results to humans is restricted, however, by uncontrolled exposure

30 conditions, small sample sizes, and other unknown exposure and nutritional factors in the studies

31 in mammals and birds, and the negative studies in rodents. They also bring up the issue of which

1   species of "sentinel" animals is more useful for predicting urban pollutant effects in humans.

2   Thus, in these field studies, it is difficult to assign a specific role to PM (or to any other

3   component of the mixture) in the significant cardiopulmonary effects reported.

4   Similar morphological changes (Calderón-Garcidueñas et al., 2000a; 2001a,b) and chest

5   X-ray evidence of mild lung hyperinflation (Calderón-Garcidueñas et al., 2000b) have been

6   reported in children residing in urban and rural areas of Mexico City. The ambient air in urban

7   areas, particularly in Southwest Metropolitan Mexico City (SWMMC), is a complex mixture of

8   particles and gases, including high concentrations of O_3 and aldehydes that previously have been

9   shown to cause airway inflammation and epithelial lesions in humans (e.g., Calderón-

10   Garcidueñas et al., 1992, 1994, 1996) and laboratory animals (Morgan et al., 1986; Heck et al.,

11   1990; Harkema et al., 1994, 1997a,b). The described effects demonstrate a persistent, ongoing

12   upper and lower airway inflammatory process and chest X-ray abnormalities in children residing

13   predominantly in SWMMC. Again, extrapolation of these results to urban populations of the

14   United States is difficult because of the unique complex of urban air in Mexico City,

15   uncontrolled exposure conditions, and other unknown exposure and nutritional factors.

16   Only one controlled study has examined the effect of a combined inhalation exposure to

17   CAPs and O_3 in human subjects. In a randomized, double-blind crossover study, Brook et al.

18   (2002) exposed 25 healthy male and female subjects, 34.9 ± 10 (SD) years of age, to filtered

19   ambient air containing 1.6 $\mu g/m^3$ $PM_{2.5}$ and 9 ppb O_3 (control) or to unfiltered air containing

20   150 $\mu g/m^3$ CAPs and 120 ppb O_3 while at rest for 2 h. Blood pressure was measured and high-

21   resolution brachial artery ultrasonography (BAUS) was performed prior to and 10 min after

22   exposure. The BAUS technique was used to measure brachial artery diameter (BAD),

23   endothelium-dependent flow-mediated dilation (FMD), and endothelial-independent

24   nitroglycerine-mediated dilation (NMD). Although no changes in blood pressure or endothelial-

25   dependent or independent dilatation were observed, a small (2.6%) but statistically significant

26   (p = 0.007) decrease in BAD was observed in CAPs plus O_3 exposures (-0.09 mm) when

27   compared to filtered air exposures (+0.01 mm). Pre-exposure BAD showed no significant day-

28   to-day variation (0.03 mm), and no significant exposure differences were found for other gaseous

29   pollutants (CO, NO_x, SO_2) in the ambient air. This finding suggests that combined exposure to a

30   mixture of CAPs and O_3 produces vasoconstriction, potentially via autonomic reflexes or as a

31   result of an increase in circulating endothelin, as has been described in rats exposed to urban PM

1   (Vincent et al., 2001). It is not known, however, whether this effect is caused by CAPS or O_3

2   alone, or if vasoactive responses would be found at lower $PM_{2.5}$ and O_3 concentrations typically

3   found in most urban locations in North America.

4   The effects of gaseous pollutants on PM-mediated responses also have been examined by in

5   vitro studies, though to a limited extent. Churg et al. (1996) demonstrated increased uptake of

6   asbestos or TiO_2 into rat tracheal explant cultures in response to 10 min O_3 (up to 1.0 ppm) pre-

7   exposure. These data suggest that low concentrations O_3 may increase the penetration of some

8   types of PM into epithelial cells. Additionally, Madden et al. (2000) demonstrated a greater

9   potency for ozonized diesel PM to induce prostaglandin E_2 production from human epithelial cell

10   cultures, suggesting that O_3 can modify the biological activity of PM derived from diesel exhaust.

11   No effect of NO_2 exposure on PM-induced interleukin-8 production by A549 epithelial cell

12   line was found (Dick et al., 2001). The PM_{10} used in this study was collected from gas stoves.

13

14

15   7.7 SUMMARY

16   7.7.1 Biological Plausibility

17   Toxicological studies can play an integral role in answering the following two key

18   questions regarding biological plausibility of PM health effects.

19   (1) What component (or components) of ambient PM cause health effects?

20   (2) Are the statistical associations between PM and health effects biologically plausible?

21   This summary focuses on the progress that toxicological studies have made towards answering

22   these questions.

23

24   7.7.1.1 Link Between Specific Particulate Matter Components and Health Effects

25   Key to the validity of the biological plausibility is the need to understand the linkage

26   between the components of airborne PM responsible for the adverse effects and the individuals at

27   risk. The plausibility of the association between PM and increases in morbidity and mortality has

28   been questioned because the adverse cardiopulmonary effects have been observed at very low

29   PM concentrations, often below the current NAAQS for PM_{10}. To date, toxicology studies on

30   PM have provided only very limited evidence for specific PM components being responsible for

1   observed cardiopulmonary effects of ambient PM. Studies have shown that some components of

2   particles are more toxic than others. For example, high concentrations of ROFA and associated

3   soluble metals have produced clinically significant effects (including death) in compromised

4   animals. The relevance of these findings to understanding the adverse effects of PM components

5   is tempered, however, by the large difference between metal concentrations delivered to the test

6   animals and metal concentrations present in the ambient urban environment. Such comparisons

7   must be applied to the interpretation of all studies that examine the individual components of

8   ambient urban PM. A summary of potential contributions of individual physical/chemical factors

9   of particles to cardiopulmonary effects is given below.

10

11   *Acid Aerosols*

12   There is relatively little new information on the effects of acid aerosols, and the conclusions

13   of the 1996 PM AQCD are unchanged. It was previously concluded that acid aerosols cause

14   little or no change in pulmonary function in healthy subjects, but asthmatics may develop small

15   changes in pulmonary function. This conclusion is supported by the recent study of Linn and

16   colleagues (1997) in which children (26 children with allergy or asthma and 15 healthy children)

17   were exposed to sulfuric acid aerosol (100 μg/m^3) for 4 h. There were no significant effects on

18   symptoms or pulmonary function when data from the entire group was analyzed, but the allergy

19   group had a significant increase in symptoms after the acid aerosol exposure.

20   Although pulmonary effects of acid aerosols have been the subject of extensive research in

21   past decades, the cardiovascular effects of acid aerosols have received little attention. Zhang

22   et al. (1997) reported that inhalation of acetic acid fumes caused reflex-mediated increases in

23   blood pressure in normal and spontaneously hypertensive rats. Thus, acid components should

24   not be ruled out as possible mediators of PM health effects. In particular, the cardiovascular

25   effects of acid aerosols at realistic concentrations need further investigation.

26

27   *Metals*

28   The previous PM AQCD (U.S. Environmental Protection Agency, 1996a) mainly relied on

29   data related to occupational exposures to evaluate the potential toxicity of metals in particulate

30   air pollution. Since that time, in vivo and in vitro studies using ROFA or soluble transition

31   metals have contributed substantial new information on the health effects of particle-associated

1   soluble metals. Although there are some uncertainties about differential effects of one transition

2   metal versus another, water soluble metals leached from ROFA have been shown consistently

3   (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro and in vivo.

4   Even though it is clear that combustion particles that have a high content of soluble metals

5   can cause lung injury and even death in compromised animals, it has not been established that the

6   small quantities of metals associated with ambient PM are sufficient to cause health effects.

7   Moreover, it cannot be assumed that metals are the primary toxic component of ambient PM.

8   In studies in which various ambient and emission source particulates were instilled into rats, the

9   soluble metal content did appear to be the primary determinant of lung injury (Costa and Dreher,

10   1997). However, one published study has compared the effects of inhaled ROFA (at 1 mg/m^3) to

11   concentrated ambient PM (four experiments, at mean concentrations of 475 to 900 μg/m^3) in

12   normal and SO_2-induced bronchitic rats. A statistically significant increase in at least one lung

13   injury marker was seen in bronchitic rats with only one out of four of the concentrated ambient

14   exposures; whereas inhaled ROFA had no effect even though the content of soluble iron,

15   vanadium, and nickel was much higher in the ROFA sample than in the concentrated ambient

16   PM.

17

18   *Ultrafine Particles*

19   When this subject was reviewed in the 1996 PM AQCD (U. S. Environmental Protection

20   Agency, 1996a), it was not known whether the pulmonary toxicity of freshly generated ultrafine

21   teflon particles was due to particle size or a result of absorbed fumes. Subsequent studies with

22   other types of ultrafine particles have shown that the chemical constituents of ultrafines

23   substantially modulate their toxicity. For example, Kuschner et al. (1997) have established that

24   inhalation of MgO particles produces far fewer respiratory effects than does ZnO. Also,

25   inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge

26   (100 μg/m^3 for 6 h) caused minimal lung inflammation (Elder et al., 2000a,b), compared to

27   ultrafine Teflon or metal particles. On the other hand, instillation of 125 μg of ultrafine carbon

28   black (20 nm) caused substantially more inflammation than did the same dose of fine particles of

29   carbon black (200 to 250 nm), suggesting that ultrafine particles may cause more inflammation

30   than larger particles (Li et al., 1997). However, the chemical constituents of the two sizes of

31   carbon black used in this study were not analyzed, and it cannot be assumed that the chemical

1 composition was the same for the two sizes. Thus, there is still insufficient toxicological

2 evidence to conclude that ambient concentrations of ultrafine particles contribute to the health

3 effects of particulate air pollution. With acid aerosols, studies of low concentrations of sulfuric

4 acid ultrafine metal oxide particles have demonstrated effects in the lung. However, it is possible

5 that inhaled ultrafine particles may have systemic effects that are independent of effects on the

6 lung.

7

8 *Bioaerosols*

9 Recent studies support the conclusion of the 1996 PM AQCD (U. S. Environmental

10 Protection Agency, 1996a), which stated that bioaerosols, at concentrations present in the

11 ambient environment, would not account for the reported health effects of ambient PM.

12 Dose-response studies in healthy volunteers exposed to 0.55 and 50 μg endotoxin, by the

13 inhalation route, showed a threshold for pulmonary and systemic effects for endotoxin between

14 0.5 and 5.0 μg (Michel et al., 1997). Monn and Becker (1999) examined effects of size

15 fractionated outdoor PM on human monocytes and found cytokine induction characteristic of

16 endotoxin activity in the coarse-size fraction but not in the fine fraction. Available information

17 suggests that ambient concentrations of endotoxin are very low and do not exceed 0.5 ng/m^3.

18

19 *Diesel Exhaust Particles*

20 As described in Section 7.2.1.2, there is growing toxicological evidence that diesel PM

21 exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has

22 been linked to eosinophil degranulation and induction of cytokine production, suggesting that the

23 organic constituents of diesel PM are the responsible part for the immune effects. It is not known

24 whether the adjuvant-like activity of diesel PM is unique or whether other combustion particles

25 have similar effects. It is important to compare the immune effects of other source-specific

26 emissions, as well as concentrated ambient PM, to diesel PM to determine the extent to which

27 exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and

28 asthma.

Organic Compounds

Published research on the acute effects of particle-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles. Like metals, organics are common constituents of combustion-generated particles and have been found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial portion of the mass of ambient PM (10 to 60% of the total dry mass [Turpin, 1999]). The organic fraction of ambient PM has been evaluated for its mutagenic effects. Although the organic fraction of ambient PM is a poorly characterized heterogeneous mixture of an unknown number of different compounds, strategies have been proposed for examining the health effects of this potentially important constituent (Turpin, 1999).

Ambient Particle Studies

Ambient particle studies should be the most relevant in understanding the susceptibility of individuals to PM and the underlying mechanisms. Studies have used collected urban PM for intratracheal administration to healthy and compromised animals. Despite the difficulties in extrapolating from the bolus delivery used in such studies, they have provided strong evidence that the chemical composition of ambient particles can have a major influence on toxicity. More recent work with inhaled concentrated ambient PM has observed cardiopulmonary changes in rodents and dogs at high concentrations of fine PM. No comparative studies to examine the effects of ultrafine and coarse ambient PM have been done, although a new ambient particle concentrator developed by Sioutas and colleagues should permit the direct toxicological comparison of various ambient particle sizes. Importantly, it has become evident that, although the concentrated ambient PM studies can provide important dose-response information, identify susceptibility factors in animal models, and permit examination of mechanisms related to PM toxicity, they are not particularly well suited for the identification of toxic components in urban PM. Because only a limited number of exposures using concentrated ambient PM can be reasonably conducted by a given laboratory in a particular urban environment, there may be insufficient information to conduct a factor analysis on an exposure/response matrix. This may also hinder principal component analysis techniques that are useful in identifying particle components responsible for adverse outcomes.

7.7.1.2 Susceptibility

Progress has been made in understanding the role of individual susceptibility to ambient PM effects. Studies have consistently shown that older animals or animals with certain types of compromised health, either genetic or induced, are more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models has created problems. Moreover, because PM seems to affect broad categories of disease states, ranging from cardiac arrhythmias to pulmonary infection, it can be difficult to know what disease models to use in understanding the biological plausibility of the adverse health effects of PM. Thus, the identification of susceptible animal models has been somewhat slow, but overall it represents solid progress when one considers that data from millions of people are necessary in epidemiology studies to develop the statistical power to detect small increases in PM-related morbidity and mortality.

7.7.2 Mechanisms of Action

The mechanisms that underlie the biological responses to ambient PM are not clear. Various toxicologic studies using particulate matter having diverse physicochemical characteristics have shown that these characteristics have a great impact on the specific response that is observed. Thus, there are multiple biological mechanisms that may be responsible for observed morbidity/mortality due to exposure to ambient PM, and these mechanisms may be highly dependent on the type of particle in the exposure atmosphere. However, it should be noted that many controlled exposure studies used particle concentrations much higher than those typically occurring in ambient air. Thus, some of the mechanisms elicited may not occur with exposure to lower levels. Clearly, controlled exposure studies have not as yet been able to unequivocally determine the particle characteristics and the toxicological mechanisms by which ambient PM may affect biological systems.

REFERENCES

Adamson, I. Y. R.; Prieditis, H.; Hedgecock, C.; Vincent. R. (2000) Zinc is the toxic factor in the lung response to an atmospheric particulate sample. Toxicol. Appl. Pharmacol. 166: 111-119.

Amdur, M. O.; Chen, L. C. (1989) Furnace-generated acid aerosols: speciation and pulmonary effects. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 147-150.

Amdur, M. O.; Dubriel, M.; Creasia, D. A. (1978) Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

Ball, B. R.; Smith, K. R.; Veranth, J. M.; Aust, A. E. (2000) Bioavailability of iron from coal fly ash: mechanisms of mobilization and of biological effects. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 209-225.

Bayram, H.; Devalia, J. L.; Khair, O. A.; Abdelaziz, M. M.; Sapsford, R. J.; Sagai, M.; Davies, R. J. (1998a) Comparison of ciliary activity and inflammatory mediator release from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients and the effect of diesel exhaust particles *in vitro*. J. Allergy Clin. Immunol. 102: 771-782.

Bayram, H.; Devalia, J. L.; Sapsford, R. J.; Ohtoshi, T.; Miyabara, Y.; Sagai, M.; Davies, R. J. (1998b) The effect of diesel exhaust particles on cell function and release of inflammatory mediators from human bronchial epithelial cells *in vitro*. Am. J. Respir. Cell Mol. Biol. 18: 441-448.

Becker, S.; Soukup, J. M. (1998) Decreased CD11B expression, phagocytosis, and oxidative burst in urban particulate pollution-exposed human monocytes and alveolar macrophages. J. Toxicol. Environ. Health Part A 55: 455-477.

Becker, S.; Soukup, J. M.; Gilmour, M. I.; Devlin, R. B. (1996) Stimulation of human and rat alveolar macrophages by urban air particulates: effects on oxidant radical generation and cytokine production. Toxicol. Appl. Pharmacol. 141: 637-648.

Blomberg, A.; Sainsbury, C.; Rudell, B.; Frew, A. J.; Holgate, S. T.; Sandström, T.; Kelly, F. J. (1998) Nasal cavity lining fluid ascorbic acid concentration increases in healthy human volunteers following short term exposure to diesel exhaust. Free Radical Res. 28: 59-67.

Bolarin, D. M.; Bhalla, D. K.; Kleinman, M. T. (1997) Effects of repeated exposures of geriatric rats to ozone and particle-containing atmospheres: an analysis of bronchoalveolar lavage and plasma proteins. Inhalation Toxicol. 9: 423-434.

Bonner, J. C.; Rice, A. B.; Lindroos, P. M.; O'Brien, P. O.; Dreher, K. L.; Rosas, I.; Alfaro-Moreno, E.; Osornio-Vargas, A. R. (1998) Induction of the lung myofibroblast PDGF receptor system by urban ambient particles from Mexico City. Am. J. Respir. Cell Mol. Biol. 19: 672-680.

Bouthillier, L.; Vincent, R.; Goegan, P.; Adamson, I. Y. R.; Bjarnason, S.; Stewart, M.; Guénette, J.; Potvin, M.; Kumarathasan, P. (1998) Acute effects of inhaled urban particles and ozone: lung morphology, macrophage activity, and plasma endothelin-1. Am. J. Pathol. 153: 1873-1884.

Brain, J. D.; Long, N. C.; Wolfthal, S. F.; Dumyahn, T.; Dockery, D. W. (1998) Pulmonary toxicity in hamsters of smoke particles from Kuwaiti oil fires. Environ. Health Perspect. 106: 141-146.

Broeckaert, F.; Buchet, J. P.; Huaux, F.; Lardot, C.; Lison, D.; Yager, J. W. (1997) Reduction of the ex vivo production of tumor necrosis factor alpha by alveolar phagocytes after administration of coal fly ash and copper smelter dust. J. Toxicol. Environ. Health 51: 189-202.

Brook, R. D.; Brook, J. R.; Urch, B.; Vincent, R.; Rajagopalan, S.; Silverman, F. (2002) Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in health adults. Circulation 105: 1534-1536.

Calderón-Garcidueñas, L.; Osorno-Velaquez, A.; Bravo-Alvarez, H.; Delgado-Chavez, R.; Barrios-Marquez, R. (1992) Histopathologic changes of the nasal mucosa in southwest metropolitan Mexico City inhabitants. Am. J. Pathol. 140: 225-232.

Calderón-Garcidueñas, L.; Rodríguez-Alcaraz, A.; García, R.; Sanchez, G.; Barragan, G.; Camacho, R.; Ramirez, L. (1994) Human nasal mucosal changes after exposure to urban pollution. Environ. Health Perspect. 102: 1074-1080.

Calderón-Garcidueñas, L.; Rodríguez-Alcaraz, A.; García, R.; Ramirez, L.; Barragan, G. (1995) Nasal inflammatory responses in children exposed to a polluted urban atmosphere. J. Toxicol. Environ. Health 45: 427-437.

Calderón-Garcidueñas, L.; Osnaya-Brízuela, N.; Ramirez-Martínez, L.; Villarreal-Calderón, A. (1996) DNA strand breaks in human nasal respiratory epithelium are induced upon exposure to urban pollution. Environ. Health Perspect. 104: 160-168.

Calderón-Garcidueñas, L.; Devlin, R. B.; Miller, F. J. (2000a) Respiratory tract pathology and cytokine imbalance in clinically healthy children chronically and sequentially exposed to air pollutants. Med. Hypotheses 55: 373-378.

Calderón-Garcidueñas, L.; Mora-Tascareño, A.; Chung, C. J.; Valencia, G.; Fordham, L. A.; García, R.; Osnaya, N.; Romero, L.; Acuña, H.; Villarreal-Calderón, A.; Devlin, R. B.; Koren, H. S. (2000b) Exposure to air pollution is associated with lung hyperinflation in healthy children and adolescents in southwest Mexico City: a pilot study. Inhalation Toxicol. 12: 537-561.

Calderón-Garcidueñas, L.; Valencia-Salazar, G.; Rodríguez-Alcaraz, A.; Gambling, T. M.; García, R.; Osnaya, N.; Villarreal-Calderón, A.; Devlin, R. B.; Carson, J. L. (2001a) Ultrastructural nasal pathology in children chronically and sequentially exposed to air pollutants. Am. J. Respir. Cell Mol. Biol. 24: 132-138.

Calderón-Garcidueñas, L.; Rodríguez-Alcaraz, A.; Valencia-Salazar, G.; Mora-Tascareño, A.; García, R.; Osnaya, N.; Villarreal-Calderón, A.; Devlin, R. B.; Van Dyke, T. L. (2001b) Nasal biopsies of children exposed to air pollutants. Toxicol. Pathol. 29: 558-564.

Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Fordham, L. A.; Chung, C. J.; García, R.; Osnaya, N.; Hernández, J.; Acuña, H.; Gambling, T. M.; Villarreal-Calderón, A.; Carson, J.; Koren, H. S.; Devlin, R. B. (2001c) Canines as sentinel species for assessing chronic exposures to air pollutants: part 1. respiratory pathology. Toxicol. Sci. 61: 342-355.

Calderón-Garcidueñas, L.; Gambling, T. M.; Acuña, H.; García, R.; Osnaya, N.; Monroy, S.; Villarreal-Calderón, A.; Carson, J.; Koren, H. S.; Devlin, R. B. (2001d) Canines as sentinel species for assessing chronic exposures to air pollutants: part 2. cardiac pathology. Toxicol. Sci. 61: 356-367.

Campen, M. J.; Costa, D. L.; Watkinson, W. P. (2000) Cardiac and thermoregulatory toxicity of residual oil fly ash in cardiopulmonary-compromised rats. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 7-22.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Evansky, P. A.; Costa, D. L.; Watkinson, W. P. (2001) Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol. Sci. 64: 243-252.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Costa, D. L.; Watkinson, W. P. (2002) Cardiac and thermoregulatory effects of instilled particulate matter-associated transition metals in healthy and cardiopulmonary-compromised rats. J. Toxicol. Environ. Health (special issue): in press.

Carter, J. D.; Ghio, A. J.; Samet, J. M.; Devlin, R. B. (1997) Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. Toxicol. Appl. Pharmacol. 146: 180-188.

Castellan, R. M.; Olenchock, S. A.; Hankinson, J. L.; Millner, P. D.; Cocke, J. B.; Bragg, C. K.; Perkins, H. H., Jr.; Jacobs, R. R. (1984) Acute bronchoconstriction induced by cotton dust: dose-related responses to endotoxin and other dust factors. Ann. Intern. Med. 102: 157-163.

Castellan, R. M.; Olenchock, S. A.; Kinsley, K. B.; Hankinson, J. L. (1987) Inhaled endotoxin and decreased spirometric values: an exposure-response relation for cotton dust. N. Engl. J. Med. 317: 605-610.

Chang, M. C.; Sioutas, C.; Kim, S.; Gong, H., Jr.; Linn, W. S. (2000) Reduction of nitrate losses from filter and impactor samplers by means of concentration enrichment. Atmos. Environ. 34: 85-98.

Chen, L. C.; Fine, J. M.; Qu, Q.-S.; Amdur, M. O.; Gordon, T. (1992) Effects of fine and ultrafine sulfuric acid aerosols in guinea pigs: alterations in alveolar macrophage function and intracellular pH. Toxicol. Appl. Pharmacol. 113: 109-117.

Chen, L. C.; Fang, C. P.; Qu, Q. S.; Fine, J. M.; Schlesinger, R. B. (1993) A novel system for the *in vitro* exposure of pulmonary cells to acid sulfate aerosols. Fundam. Appl. Toxicol. 20: 170-176.

Churg, A.; Brauer, M.; Keeling, B. (1996) Ozone enhances the uptake of mineral particles by tracheobronchial epithelial cells in organ culture. Am. J. Respir. Crit. Care Med. 153: 1230-1233.

Churg, A.; Stevens, B.; Wright, J. L. (1998) Comparison of the uptake of fine and ultrafine TiO_2 in a tracheal explant system. Am. J. Physiol. 274: L81-L86.

Clarke, R. W.; Catalano, P. J.; Koutrakis, P.; Krishna Murthy, G. G.; Sioutas, C.; Paulauskis, J.; Coull, B.; Ferguson, S.; Godleski, J. J. (1999) Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. Inhalation Toxicol. 11: 637-656.

Clarke, R. W.; Coull, B.; Reinisch, U.; Catalano, P.; Killingsworth, C. R.; Koutrakis, P.; Kavouras, I.; Murthy, G. G. K.; Lawrence, J.; Lovett, E.; Wolfson, J. M.; Verrier, R. L.; Godleski, J. J. (2000a) Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. Environ. Health Perspect. 108: 1179-1187.

Clarke, R. W.; Catalano, P.; Coull, B.; Koutrakis, P.; Krishna Murthy, G. G.; Rice, T.; Godleski, J. J. (2000) Age-related responses in rats to concentrated urban air particles (CAPs). In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 73-84.

Cohen, M. D.; Becker, S.; Devlin, R.; Schlesinger, R. B.; Zelikoff, J. T. (1997) Effects of vanadium upon polyl:C-induced responses in rat lung and alveolar macrophages. J. Toxicol. Environ. Health 51: 591-608.

Cormier, Y.; Laviolette, M.; Bedard, G.; Dosman, J.; Israel-Assayag, E. (1998) Effect of route of breathing on response to exposure in a swine confinement building. Am. J. Respir. Crit. Care Med. 157: 1512-1521.

Costa, D. L.; Dreher, K. L. (1997) Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1053-1060.

Creutzenberg, O.; Bellmann, B.; Muhle, H.; Dasenbrock, C.; Morrow, P.; Mermelstein, R. (1998) Lung clearance and retention of toner, TiO_2, and crystalline silica, utilizing a tracer technique during chronic inhalation exposure in Syrian Golden hamsters. Inhalation Toxicol. 10: 731-751.

Diaz-Sanchez, D.; Tsien, A.; Casillas, A.; Dotson, A. R.; Saxon, A. (1996) Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. J. Allergy Clin. Immunol. 98: 114-123.

Diaz-Sanchez, D.; Tsien, A.; Fleming, J.; Saxon, A. (1997) Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J. Immunol. 158: 2406-2413.

Dick, C. A. J.; Dennekamp, M.; Howarth, S.; Cherrie, J. W.; Seaton, A.; Donaldson, K.; Stone, V.; (2001) Stimulation of IL-8 release from epithelial cells by gas cooker PM_{10}: a pilot study. Occup. Environ. Med. 58: 208-210.

Diociaiuti, M.; Balduzzi, M.; De Berardis, B.; Cattani, G.; Stacchini, G.; Ziemacki, G.; Marconi, A.; Paoletti, L. (2001) The two $PM_{2.5}$ (fine) and $PM_{2.5^-10}$ (coarse) fractions: evidence of different biological activity. Environ. Res. A 86: 254-262.

Donaldson, K.; Brown, D. M.; Mitchell, C.; Dineva, M.; Beswick, P. H.; Gilmour, P.; MacNee, W. (1997) Free radical activity of PM_{10}: iron-mediated generation of hydroxyl radicals. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1285-1289.

Dong, W.; Lewtas, J.; Luster, M. I. (1996) Role of endotoxin in tumor necrosis factor αexpression from alveolar macrophages treated with urban air particles. Exp. Lung Res. 22: 577-592.

Dormans, J. A. M. A.; Steerenberg, P. A.; Arts, J. H. E.; Van Bree, L.; De Klerk, A.; Verlaan, A. P. J.; Bruijntjes, J. P.; Beekhof, P.; Van Soolingen, D.; Van Loveren, H. (1999) Pathological and immunological effects of respirable coal fly ash in male wistar rats. Inhalation Toxicol. 11: 51-69.

Dreher, K. L.; Jaskot, R. H.; Lehmann, J. R.; Richards, J. H.; McGee, J. K.; Ghio, A. J.; Costa, D. L. (1997) Soluable transition metals mediate residual oil fly ash induced acute lung injury. J. Toxicol. Environ. Health 50: 285-305.

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

Dye, J. A.; Adler, K. B.; Richards, J. H.; Dreher, K. L. (1997) Epithelial injury induced by exposure to residual oil fly-ash particles: role of reactive oxygen species? Am. J. Respir. Cell Mol. Biol. 17: 625-633.

Dye, J. A.; Adler, K. B.; Richards, J. H.; Dreher, K. L. (1999) Role of soluble metals in oil fly ash-induced airway epithelial injury and cytokine gene expression. Am. J. Physiol. 277: L498-L510.

Dye, J. A.; Lehmann, J. R.; McGee, J. K.; Winsett, D. W.; Ledbetter, A. D.; Everitt, J. I.; Ghio, A. J.; Costa, D. L. (2001) Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ. Health Perspect. 109(suppl. 3): 395-403.

Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000a) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Phalen, R. F., ed. Inhalation Toxicology:

proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 85-98.

Elder, A. C. P.; Gelein, R.; Finkelstein, J. N.; Cox, C.; Oberdörster, G. (2000b) Pulmonary inflammatory response to inhaled ultrafine particles is modified by age, ozone exposure, and bacterial toxin. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 227-246.

Fabiani, R.; Pampanella, L.; Minelli, A.; Mezzasoma, I.; Vecchiarelli, A.; Morozzi, G. (1997) Effect of airborne particulate extracts on monocyte oxidative metabolism. J. Environ. Pathol. Toxicol. Oncol. 16: 195-199.

Ferin, J.; Oberdörster, G.; Penney, D. P.; Soderholm, S. C.; Gelein, R.; Piper, H. C. (1990) Increased pulmonary toxicity of ultrafine particles? I. Particle clearance, translocation, morphology. J. Aerosol Sci. 21: 381-384.

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

Finkelstein, J. N.; Johnston, C.; Barrett, T.; Oberdörster, G. (1997) Particulate-cell interactions and pulmonary cytokine expression. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1179-1182.

Folinsbee, L. J.; Kim, C. S.; Kehrl, H. R.; Prah, J. D.; Devlin, R. B. (1997) Methods in human inhalation toxicology. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press LLC; pp. 607-670.

Fortoul, T. I.; Osorio, L. S.; Tovar, A. T.; Salazar, D.; Castilla, M. E.; Olaiz-Fernández, G. (1996) Metals in lung tissue from autopsy cases in Mexico City residents: comparison of cases from the 1950s and the 1980s. Environ. Health Perspect. 104: 630-632.

Frampton, M. W.; Voter, K. Z.; Morrow, P. E.; Roberts, N. J., Jr.; Culp, D. J.; Cox, C.; Utell, M. J. (1992) Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. Am. Rev. Respir. Dis. 146: 626-632.

Frampton, M. W.; Morrow, P. E.; Cox, C.; Levy, P. C.; Condemi, J. J.; Speers, D.; Gibb, F. R.; Utell, M. J. (1995) Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. Environ. Res. 69: 1-14.

Frampton, M. W.; Ghio, A. J.; Samet, J. M.; Carson, J. L.; Carter, J. D.; Devlin, R. B. (1999) Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. Am. J. Physiol. 277: L960-L967.

Fujimaki, H.; Katayama, N.; Wakamori, K. (1992) Enhanced histamine release from lung mast cells of guinea pigs exposed to sulfuric acid aerosols. Environ. Res. 58: 117-123.

Gardner, S. Y.; Lehmann, J. R.; Costa, D. L. (2000) Oil fly ash-induced elevation of plasma fibrinogen levels in rats. Toxicol. Sci. 56: 175-180.

Gavett, S. H.; Madison, S. L.; Dreher, K. L.; Winsett, D. W.; McGee, J. K.; Costa, D. L. (1997) Metal and sulfate composition of residual oil fly ash determines airway hyperreactivity and lung injury in rats. Environ. Res. 72: 162-172.

Gavett, S. H.; Madison, S. L.; Stevens, M. A.; Costa, D. L. (1999) Residual oil fly ash amplifies allergic cytokines, airway responsiveness, and inflammation in mice. Am. J. Respir. Crit. Care Med. 160: 1897-1904.

Gearhart, J. M.; Schlesinger, R. B. (1986) Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7: 681-689.

Gercken, G.; Berg, I.; Dörger, M.; Schlüter, T. (1996) Mechanisms of particle-induced activation of alveolar macrophages. Toxicol. Lett. 88: 121-129.

Ghio, A. J.; Devlin, R. B. (2001) Inflammatory lung injury after bronchial instillation of air pollution particles. Am. J. Respir. Crit. Care Med. 164: 704-708.

Ghio, A. J.; Meng, Z. H.; Hatch, G. E.; Costa, D. L. (1997a) Luminol-enhanced chemiluminescence after in vitro exposures of rat alveolar macrophages to oil fly ash is metal dependent. Inhalation Toxicol. 9: 255-271.

Ghio, A. J.; Piantadosi, C. A.; Crumbliss, A. L. (1997b) Hypothesis: iron chelation plays a vital role in neutrophilic inflammation. BioMetals 10: 135-142.

Ghio, A. J.; Carter, J. D.; Richards, J. H.; Brighton, L. E.; Lay, J. C.; Devlin, R. B. (1998a) Disruption of normal iron homeostasis after bronchial instillation of an iron-containing particle. Am. J. Physiol. 274: L396-L403.

Ghio, A. J.; Richards, J. H.; Dittrich, K. L.; Samet, J. M. (1998b) Metal storage and transport proteins increase after exposure of the rat lung to an air pollution particle. Toxicol. Pathol. 26: 388-394.

Ghio, A. J.; Carter, J. D.; Samet, J. M.; Reed, W.; Quay, J.; Dailey, L. A.; Richards, J. H.; Devlin, R. B. (1998c) Metal-dependent expression of ferritin and lactoferrin by respiratory epithelial cells. Am. J. Physiol. 274: L728-L736.

Ghio, A. J.; Stonehuerner, J.; Dailey, L. A.; Carter, J. D. (1999a) Metals associated with both the water-soluble and insoluble fractions of an ambient air pollution particle catalyze an oxidative stress. Inhalation Toxicol. 11: 37-49.

Ghio, A. J.; Carter, J. D.; Dailey, L. A.; Devlin, R. B.; Samet, J. M. (1999b) Respiratory epithelial cells demonstrate lactoferrin receptors that increase after metal exposure. Am. J. Physiol. 276: L933-L940.

Ghio, A. J.; Stonehuerner, J.; McGee, J. K.; Kinsey, J. S. (1999c) Sulfate content correlates with iron concentrations in ambient air pollution particles. Inhalation Toxicol. 11: 293-307.

Ghio, A. J.; Kim, C.; Devlin, R. B. (2000a) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am. J. Respir. Crit. Care Med. 162: 981-988.

Ghio, A. J.; Carter, J. D.; Richards, J. H.; Crissman, K. M.; Bobb, H. H.; Yang, F. (2000b) Diminished injury in hypotransferrinemic mice after exposure to a metal-rich particle. Am. J. Physiol. 278: L1051-L1061.

Ghio, A. J.; Gilbey, J. G.; Roggli, V. L.; Richards, J. H.; McGee, J. K.; Carson, J. L.; Devlin, R. B.; Cascio, W. E. (2001) Diffuse alveolar damage after exposure to an oil fly ash. Am. J. Respir. Crit. Care Med. 164: 1514-1518.

Gift, J. S.; Faust, R. A. (1997) Noncancer inhalation toxicology of crystalline silica: exposure-response assessment. J. Exposure Anal. Environ. Epidemiol. 7: 345-358.

Gilmour, M. I.; Taylor, F. G. R.; Baskerville, A.; Wathes, C. M. (1989a) The effect of titanium dioxide inhalation on the pulmonary clearance of *Pasteurella haemolytica* in the mouse. Environ. Res. 50: 157-172.

Gilmour, M. I.; Taylor, F. G. R.; Wathes, C. M. (1989b) Pulmonary clearance of *Pasteurella haemolytica* and immune responses in mice following exposure to titanium dioxide. Environ. Res. 50: 184-194.

Gilmour, P. S.; Brown, D. M.; Lindsay, T. G.; Beswick, P. H.; MacNee, W.; Donaldson, K. (1996) Adverse health effects of PM_{10} particles: involvement of iron in generation of hydroxyl radical. Occup. Environ. Med. 53: 817-822.

Godleski, J. J.; Verrier, R. L.; Koutrakis, P.; Catalano, P. (2000) Mechanisms of morbidity and mortality from exposure to ambient air particles. Cambridge, MA: Health Effects Institute; research report no. 91.

Goldsmith, C.-A.; Frevert, C.; Imrich, A.; Sioutas, C.; Kobzik, L. (1997) Alveolar macrophage interaction with air pollution particulates. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1191-1195.

Goldsmith, C.-A. W.; Imrich, A.; Danaee, H.; Ning, Y. Y.; Kobzik, L. (1998) Analysis of air pollution particulate-mediated oxidant stress in alveolar macrophages. J. Toxicol. Environ. Health Part A 54: 529-545.

Goldsmith, C.-A. W.; Hamada, K.; Ning, Y. Y.; Qin, G.; Catalano, P.; Murthy, G. G. K.; Lawrence, J.; Kobzik, L. (1999) The effects of environmental aerosols on airway hyperresponsiveness in a murine model of asthma. Inhalation Toxicol. 11: 981-998.

Gong, H., Jr.; Sioutas, C.; Linn, W. S.; Clark, K. W.; Terrell, S. L.; Terrell, L. L.; Anderson, K. R.; Kim, S.; Chang, M.-C. (2000) Controlled human exposures to concentrated ambient fine particles in metropolitan Los Angeles: methodology and preliminary health-effect findings. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 107-119.

Gordon, T.; Nadziejko, C.; Schlesinger, R.; Chen, L. C. (1998) Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. Toxicol. Lett. 96-97: 285-288.

Gordon, T.; Nadziejko, C.; Chen, L. C.; Schlesinger, R. (2000) Effects of concentrated ambient particles in rats and hamsters: an exploratory study. Cambridge, MA: Health Effects Institute; research report no. 93.

Grabowski, G. M.; Paulauskis, J. D.; Godleski, J. J. (1999) Mediating phosphorylation events in the vanadium-induced respiratory burst of alveolar macrophages. Toxicol. Appl. Pharmacol. 156: 170-178.

Gulisano, M.; Marceddu, S.; Barbaro, A.; Pacini, A.; Buiatti, E.; Martini, A.; Pacini, P. (1997) Damage to the nasopharyngeal mucosa induced by current levels of urban air pollution: a field study in lambs. Eur. Respir. J. 10: 567-572.

Hahon, N.; Booth, J. A.; Green, F.; Lewis, T. R. (1985) Influenza virus infection in mice after exposure to coal dust and diesel engine emissions. Environ. Res. 37: 44-60.

Hamada, K.; Goldsmith, C.-A.; Kobzik, L. (1999) Increased airway hyperresponsiveness and inflammation in a juvenile mouse model of asthma exposed to air-pollutant aerosol. J. Toxicol. Environ. Health 58: 129-143.

Hamada, K.; Goldsmith, C.-A.; Goldman, A.; Kobzik, L. (2000) Resistance of very young mice to inhaled allergen sensitization Is overcome by coexposure to an air-pollutant aerosol. Am. J. Respir. Crit. Care Med. 161: 1285-1293.

Harder, S. D.; Soukup, J. M.; Ghio, A. J.; Devlin, R. B.; Becker, S. (2001) Inhalation of $PM_{2.5}$ does not modulate host defense or immune parameters in blood or lung of normal human subjects. Environ. Health Perspect. 109(suppl. 4): 599-604.

Harkema, J. R.; Morgan, K. T.; Gross, E. A.; Catalano, P. J.; Griffith, W. C. (1994) Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies. Part VII: effects on the nasal mucociliary apparatus. Cambridge, MA: Health Effects Institute; research report no. 65.

Harkema, J. R.; Barr, E. B.; Hotchkiss, J. A. (1997a) Responses of rat nasal epithelium to short- and long-term exposures of ozone: image analysis of epithelial injury, adaptation and repair. Microsc. Res. Tech. 36: 276-286.

Harkema, J. R.; Hotchkiss, J. A.; Griffith, W. C. (1997b) Mucous cell metaplasia in rat nasal epithelium after a 20-month exposure to ozone: a morphometric study of epithelial differentiation. Am. J. Respir. Cell Mol. Biol. 16: 521-530.

Health Effects Institute. (1995) Diesel exhaust: a critical analysis of emissions, exposure, and health effects: a special report of the Institute's Diesel Working Group. Cambridge, MA: Health Effects Institute.

Heck, H. d'A.; Casanova, M.; Starr, T. B. (1990) Formaldehyde toxicity--new understanding. Crit. Rev. Toxicol. 20: 397-426.

Heyder, J.; Beck-Speier, I.; Busch, B.; Dirscherl, P.; Heilmann, P.; Ferron, G. A.; Josten, M.; Karg, E.; Kreyling, W. G.; Lenz, A.-G.; Maier, K. L.; Miaskowski, U.; Platz, S.; Reitmeir, P.; Schulz, H.; Takenaka, S.; Ziesenis, A. (1999) Health effects of sulfur-related environmental air pollution. I. Executive summary. Inhalation Toxicol. 11: 343-359.

Hitzfeld, B.; Friedrichs, K. H.; Ring, J.; Behrendt, H. (1997) Airborne particulate matter modulates the production of reactive oxygen species in human polymorphonuclear granulocytes. Toxicology 120: 185-195.

Holian, A.; Hamilton, R. F., Jr.; Morandi, M. T.; Brown, S. D.; Li, L. (1998) Urban particle-induced apoptosis and phenotype shifts in human alveolar macrophages. Environ. Health Perspect. 106: 127-132.

Hunter, R. J. (1981) Zeta potential in colloid science: principles and applications. Orlando, FL: Academic Press, pp. 1-124. [Ottewill, R. H.; Rowell, R. L., eds. Colloid Science].

Imrich, A.; Ning, Y. Y.; Kobzik, L. (2000) Insoluble components of concentrated air particles mediate alveolar macrophage responses in vitro. Toxicol. Appl. Pharmacol. 167: 140-150.

Irsigler, G. B.; Visser, P. J.; Spangenberg, P. A. L. (1999) Asthma and chemical bronchitis in vanadium plant workers. Am. J. Ind. Med. 35: 366-374.

Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California, 1983-1992. Environ. Health Perspect. 105: 980-985.

Jakab, G. J. (1992) Relationship between carbon black particulate-bound formaldehyde, pulmonary antibacterial defenses, and alveolar macrophage phagocytosis. Inhalation Toxicol. 4: 325-342.

Jakab, G. J. (1993) The toxicologic interactions resulting from inhalation of carbon black and acrolein on pulmonary antibacterial and antiviral defenses. Toxicol. Appl. Pharmacol. 121: 167-175.

Jakab, G. J.; Hemenway, D. R. (1993) Inhalation coexposure to carbon black and acrolein suppresses alveolar macrophage phagocytosis and TNF-α release and modulates peritoneal macrophage phagocytosis. Inhalation Toxicol. 5: 275-289.

Jakab, G. J.; Clarke, R. W.; Hemenway, D. R.; Longphre, M. V.; Kleeberger, S. R.; Frank, R. (1996) Inhalation of acid coated carbon black particles impairs alveolar macrophage phagocytosis. Toxicol. Lett. 88: 243-248.

Jiang, N.; Dreher, K. L.; Dye, J. A.; Richards, J. H.; Martin, L. D.; Adler, K. B. (2000) Residual oil fly ash induces cytotoxicity and mucin secretion by guinea pig tracheal epithelial cells via an oxidant-mediated mechanism. Toxicol. Appl. Pharmacol. 163: 221-230.

Johnston, C. J.; Finkelstein, J. N.; Gelein, R.; Baggs, R.; Oberdörster, G. (1996) Characterization of the early pulmonary inflammatory response associated with PTFE fume exposure. Toxicol. Appl. Pharmacol. 140: 154-163.

Johnston, C. J.; Finkelstein, J. N.; Gelein, R.; Oberdörster, G. (1998) Pulmonary inflammatory responses and cytokine and antioxidant mRNA levels in the lungs of young and old C57BL/6 mice after exposure to Teflon fumes. Inhalation Toxicol. 10: 931-953.

Kadiiska, M. B.; Mason, R. P.; Dreher, K. L.; Costa, D. L.; Ghio, A. J. (1997) *In vivo* evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. Chem. Res. Toxicol. 10: 1104-1108.

Kennedy, T.; Ghio, A. J.; Reed, W.; Samet, J.; Zagorski, J.; Quay, J.; Carter, J.; Dailey, L.; Hoidal, J. R.; Devlin, R. B. (1998) Copper-dependent inflammation and nuclear factor-κB activation by particulate air pollution. Am. J. Respir. Cell Mol. Biol. 19: 366-378.

Killingsworth, C. R.; Alessandrini, F.; Krishna Murthy, G. G.; Catalano, P. J.; Paulauskis, J. D.; Godleski, J. J. (1997) Inflammation, chemokine expression, and death in monocrotaline-treated rats following fuel oil fly ash inhalation. Inhalation Toxicol. 9: 541-565.

Kim, S.; Chang, M.-C.; Kim, D.; Sioutas, C. (2000a) A new generation of portable coarse, fine, and ultrafine particle concentrators for use in inhalation toxicology. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12 (suppl. 1): 121-137.

Kim, S.; Sioutas, C.; Chang, M.-C.; Gong, H., Jr. (2000b) Factors affecting the stability of the performance of ambient fine-particle concentrators. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 281-298.

Kimmel, T. A.; Chen, L. C.; Bosland, M. C.; Nadziejko, C. (1997) Influence of acid aerosol droplet size on structural changes in the rat lung caused by acute exposure to sulfuric acid and ozone. Toxicol. Appl. Pharmacol. 144: 348-355.

Kitabatake, M.; Imai, M.; Kasama, K.; Kobayashi, I.; Tomita, Y.; Yoshida, K. (1979) Effects of air pollutants on the experimental induction of asthma attacks in guinea pigs: sulfuric acid mist and mixture of the mist and sulfur dioxide. Mie Med. J. 29: 29-36.

Kleeberger, S. R.; Levitt, R. C.; Zhang, L.-Y.; Longphre, M.; Harkema, J.; Jedlicka, A.; Eleff, S. M.; DiSilvestre, D.; Holroyd, K. J. (1997) Linkage analysis of susceptibility to ozone-induced lung inflammation in inbred mice. Nat. Genet. 17: 475-478.

Kleinman, M. T.; Leaf, D. A.; Kelly, E.; Caiozzo, V.; Osann, K.; O'Niell, T. (1998) Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch. Environ. Health 53: 388-397.

Kleinman, M. T.; Mautz, W. J.; Bjarnason, S. (1999) Adaptive and non-adaptive responses in rats exposed to ozone, alone and in mixtures, with acidic aerosols. Inhalation Toxicol. 11: 249-264.

Kleinman, M. T.; Bufalino, C.; Rasmussen, R.; Hyde, D.; Bhalla, D. K.; Mautz, W. J. (2000) Toxicity of chemical components of ambient fine particulate matter ($PM_{2.5}$) inhaled by aged rats. J. Appl. Toxicol. 20: 357-364.

Knox, R. B.; Suphioglu, C.; Taylor, P.; Desai, R.; Watson, H. C.; Peng, J. L.; Bursill, L. A. (1997) Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. Clin. Exp. Allergy 27: 246-251.

Kobzik, L. (1995) Lung macrophage uptake of unopsonized environmental particulates: role of scavenger-type receptors. J. Immunol. 155: 367-376.

Kobzik, L.; Goldsmith, C.-A. W.; Ning, Y. Y.; Qin, G.; Morgan, B.; Imrich, A.; Lawrence J.; Murthy, G. G. K.; Catalano, P. J. (2001) Effects of combined ozone and air pollution particle exposure in mice. Boston, MA: Health Effects Institute; research report no. 106. Available: http://www.healtheffects.org/pubs-recent.htm [11 April 2002].

Kodavanti, U. P.; Costa, D. L. (1999) Animal models to study for pollutant effects. In: Holgate, S. T.; Samet, J. M.; Koren, H. S.; Maynard, R. L., eds. Air pollution and health. New York, NY: Academic Press; pp. 165-197.

Kodavanti, U. P.; Jaskot, R. H.; Bonner, J.; Badgett, A.; Dreher, K. L. (1996) Eosinophilic lung inflammation in particulate-induced lung injury: technical consideration in isolating RNA for gene expression studies. Exp. Lung Res. 22: 541-554.

Kodavanti, U. P.; Jaskot, R. H.; Su, W. Y.; Costa, D. L.; Ghio, A. J.; Dreher, K. L. (1997a) Genetic variability in combustion particle-induced chronic lung injury. Am. J. Physiol. 272: L521-L532.

Kodavanti, U. P.; Jaskot, R. H.; Costa, D. L.; Dreher, K. L. (1997b) Pulmonary proinflammatory gene induction following acute exposure to residual oil fly ash: roles of particle-associated metals. Inhalation Toxicol. 9: 679-701.

Kodavanti, U. P.; Hauser, R.; Christiani, D. C.; Meng, Z. H.; McGee, J.; Ledbetter, A.; Richards, J.; Costa, D. L. (1998a) Pulmonary responses to oil fly ash particles in the rat differ by virtue of their specific soluble metals. Toxicol. Sci. 43: 204-212.

Kodavanti, U. P.; Costa, D. L.; Bromberg, P. A. (1998b) Rodent models of cardiopulmonary disease: their potential applicability in studies of air pollutant susceptibility. Environ. Health Perspect. 106(suppl. 1): 111-130.

Kodavanti, U. P.; Jackson, M. C.; Ledbetter, A. D.; Richards, J. R.; Gardner, S. Y.; Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1999) Lung injury from intratracheal and inhalation exposures to residual oil fly ash in a

rat model of monocrotaline-induced pulmonary hypertension. J. Toxicol. Environ. Health Part A 57: 101-121.

Kodavanti, U. P.; Mebane, R.; Ledbetter, A.; Krantz, T.; McGee, J.; Jackson, M. C.; Walsh, L.; Hilliard, H.; Chen, B. Y.; Richards, J.; Costa, D. L. (2000a) Variable pulmonary responses from exposure to concentrated ambient air particles in a rat model of bronchitis. Toxicol. Sci. 54: 441-451.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Watkinson, W. P.; Campen, M. J.; Winsett, D. W.; Richards, J. R.; Crissman, K. M.; Hatch, G. E.; Costa, D. L. (2000b) The spontaneously hypertensive rat as a model of human cardiovascular disease: evidence of exacerbated cardiopulmonary injury and oxidative stress from inhaled emission particulate matter. Toxicol. Appl. Pharmacol. 164: 250-263.

Kodavanti, U. P.; Schladweiler, M. C. J.; Richards, J. R.; Costa, D. L. (2001) Acute lung injury from intratracheal exposure to fugitive residual oil fly ash and its constituent metals in normo- and spontaneously hypertensive rats. Inhalation Toxicol. 13: 37-54.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; McGee, J.; Richards, J. R.; Costa, D. L. (2002) Temporal association between pulmonary and systemic effects of particulate matter in healthy and cardiovascular compromised rats. J. Toxicol. Environ. Health: in press.

Kuschner, W. G.; Wong, H.; D'Alessandro, A.; Quinlan, P.; Blanc, P. D. (1997) Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles. Environ. Health Perspect. 105: 1234-1237.

Lambert, A. L.; Dong, W.; Winsett, D. W.; Selgrade, M. K.; Gilmour, M. I. (1999) Residual oil fly ash exposure enhances allergic sensitization to house dust mite. Toxicol. Appl. Pharmacol. 158: 269-277.

Lambert, A. L.; Dong, W.; Selgrade, M. K.; Gilmour, M. I. (2000) Enhanced allergic sensitization by residual oil fly ash particles is mediated by soluble metal constituents. Toxicol. Appl. Pharmacol. 165: 84-93.

Last, J. A.; Pinkerton, K. E. (1997) Chronic exposure of rats to ozone and sulfuric acid aerosol: biochemical and structural responses. Toxicology 116: 133-146.

Last, J. A.; Hyde, D. M.; Chang, D. P. Y. (1984) A mechanism of synergistic lung damage by ozone and a respirable aerosol. Exp. Lung Res. 7: 223-235.

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

Lay, J. C.; Zeman, K. L.; Ghio, A. J.; Bennett, W. D. (2001) Effects of inhaled iron oxide particles on alveolar epithelial permeability in normal subjects. Inhalation Toxicol. 13: 1065-1078.

Leduc, D.; Fally, S.; De Vuyst, P.; Wollast, R.; Yernault, J.-C. (1995) Acute exposure to realistic acid fog: effects on respiratory function and airway responsiveness in asthmatics. Environ. Res. 71: 89-98.

Lee, M. M.; Green, F. H. Y.; Roth, S. H.; Karkhanis, A.; Bjarnason, S. G.; Schürch, S. (1999) Sulfuric acid aerosol induces changes in alveolar surface tension in the guinea pig but not in the rat. Exp. Lung Res. 25: 229-244.

Leikauf, G. D.; McDowell, S. A.; Gammon, K.; Wesselkamper, S. C.; Bachurski, C. J.; Puga, A.; Wiest, J. S.; Leikauf, J. E.; Prows, D. R. (2000) Functional genomics of particle-induced lung injury. Inhalation Toxicol. 12: 59-73.

Leikauf, G.; McDowell, S. A.; Wesselkamper, S. C.; Miller, C. R.; Hardie, W. D.; Gammon, K.; Biswas, P. P.; Korfhagen, T. R.; Bachurski, C. J.; Wiest, J. S.; Willeke, K.; Bingham, E.; Leikauf, J. E.; Aronow, B. J.; Prows, D. R. (2001) Pathogenomic mechanisms for particulate matter induction of acute lung injury and inflammation in mice. Boston, MA: Health Effects Institute; research report no. 105. Available: http://www.healtheffects.org/pubs-recent.htm [11 April 2002].

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1996) Free radical activity and pro-inflammatory effects of particulate air pollution (PM_{10}) *in vivo* and *in vitro*. Thorax 51: 1216-1222.

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1997) *In vivo* and *in vitro* proinflammatory effects of particulate air pollution (PM_{10}). In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1279-1283.

Li, X. Y.; Brown, D.; Smith, S.; MacNee, W.; Donaldson, K. (1999) Short-term inflammatory responses following intratracheal instillation of fine and ultrafine carbon black in rats. Inhalation Toxicol. 11: 709-731.

Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Avol, E. L.; Hackney, J. D. (1994) Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. Am. J. Respir. Crit. Care Med. 150: 431-440.

Linn, W. S.; Gong, H., Jr.; Shamoo, D. A.; Anderson, K. R.; Avol, E. L. (1997) Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. Arch. Environ. Health 52: 179-187.

Lippmann, M. (2000) Environmental toxicants: human exposures and their health effects. 2nd ed. New York, NY: Wiley-Interscience.

Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County, California. Environ. Health Perspect. 105: 216-222.

Lison, D.; Lardot, C.; Huaux, F.; Zanetti, G.; Fubini, B. (1997) Influence of particle surface area on the toxicity of insoluble manganese dioxide dusts. Arch. Toxicol. 71: 725-729.

Long, C. M.; Suh, H. H.; Kobzik, L.; Catalano, P. J.; Ning, Y. Y.; Koutrakis, P. (2001) A pilot investigation of the relative toxicity of indoor and outdoor fine particles: *in vitro* effects of endotoxin and other particulate properties. Environ. Health Perspect. 109: 1019-1026.

Longphre, M.; Li, D.; Matovinovic, E.; Gallup, M.; Samet, J. M.; Basbaum, C. B. (2000) Lung mucin production is stimulated by the air pollutant residual oil fly ash. Toxicol. Appl. Pharmacol. 162: 86-92.

Lorz, C.; López, J. (1997) Incidence of air pollution in the pulmonary surfactant system of the pigeon (*Columbia livia*). Anat. Rec. 249: 206-212.

Madden, M. C.; Thomas, M. J.; Ghio, A. J. (1999) Acetaldehyde (CH_3CHO) production in rodent lung after exposure to metal-rich particles. Free Radical Biol. Med. 26: 1569-1577.

Madden, M. C.; Richards, J. H.; Dailey, L. A.; Hatch, G. E.; Ghio, A. J. (2000) Effect of ozone on diesel exhaust particle toxicity in rat lung. Toxicol. Appl. Pharmacol. 168: 140-148.

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

Mauderly, J. L. (1993) Toxicological approaches to complex mixtures. Environ. Health Perspect. Suppl. 101(4): 155-165.

Mautz, W. J.; Kleinman, M. T.; Bhalla, D. K.; Phalen, R. F. (2001) Respiratory tract responses to repeated inhalation of an oxidant and acid gas-particle air pollutant mixture. Toxicol. Sci. 61: 331-341.

McDowell, S. A.; Gammon, K.; Bachurski, C. J.; Weist, J. S.; Leikauf, J. E.; Prows, D. R. Leikauf, G. D. (2000) Differential gene expression in the initiation and progression of nickel-induced acute lung injury. Am. J. Respir. Cell Mol. Biol. 23: 466-474.

McKenna, I. M.; Gordon, T.; Chen, L. C.; Anver, M. R.; Waalkes, M. P. (1998) Expression of metallothionein protein in the lungs of Wistar rats and C57 and DBA mice exposed to cadmium oxide fumes. Toxicol. Appl. Pharmacol. 153: 169-178.

Menetrez, M. Y.; Foarde, K. K.; Ensor, D. S. (2001) An analytical method for the measurement of nonviable bioaerosols. J. Air Waste Manage. Assoc. 51: 1436-1442.

Michel, O.; Nagy, A.-M.; Schroeven, M.; Duchateau, J.; Nève, J.; Fondu, P.; Sergysels, R. (1997) Dose-response relationship to inhaled endotoxin in normal subjects. Am. J. Respir. Crit. Care Med. 156: 1157-1164.

Monn, C.; Becker, S. (1999) Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine ($PM_{2.5}$) and coarse particles ($PM_{10-2.5}$) in outdoor and indoor air. Toxicol. Appl. Pharmacol. 155: 245-252.

Morgan, K. T.; Patterson, D. L.; Gross, E. A. (1986) Responses of the nasal mucociliary apparatus of F-344 rats to formaldehyde gas. Toxicol. Appl. Pharmacol. 82: 1-13.

Moss, O. R.; Gross, E. A.; James, R. A.; Janszen, D. B.; Ross, P. W.; Roberts, K. C.; Howard, A. M.; Harkema, J. R.; Calderón-Garcidueñas, L.; Morgan, K. T. (2001) Respiratory tract toxicity in rats exposed to Mexico City air. Cambridge, MA: Health Effects Institute; research report no. 100. Available: http://www.healtheffects.org/ [31 July, 2001].

Muggenburg, B. A.; Barr, E. B.; Cheng, Y. S.; Seagrave, JC.; Tilley, L. P.; Mauderly, J. L. (2000) Effect of inhaled residual oil fly ash on the electrocardiogram of dogs. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 189-208.

Mukae, H.; Hogg, J. C.; English, D.; Vincent, R.; Van Eeden, S. F. (2000) Phagocytosis of particulate air pollutants by human alveolar macrophages stimulates the bone marrow. Am. J. Physiol. 279: L924-L931.

Mukae, H.; Vincent, R.; Quinlan, K.; English, D.; Hards, J.; Hogg, J. C.; Van Eeden, S. F. (2001) The effect of repeated exposure to particulate air pollution (PM_{10}) on the bone marrow. Am. J. Respir. Crit. Care Med. 163: 201-209.

Murphy, S. A.; BéruBé, K. A.; Pooley, F. D.; Richards, R. J. (1998) The response of lung epithelium to well characterised fine particles. Life Sci. 62: 1789-1799.

Nadadur, S. S.; Kodavanti, U. P. (2002) Altered gene expression profiles of rat lung in response to an emission particulate and its metal constituents. J. Toxicol. Environ. Health: in press.

Nadadur, S. S.; Schladweiler, M. C. J.; Kodavanti, U. P. (2000) A pulmonary rat gene array for screening altered expression profiles in air pollutant-induced lung injury. Inhalation Toxicol. 12: 1239-1254.

Nadeau, D.; Vincent, R.; Kumarathasan, P.; Brook, J.; Dufresne, A. (1996) Cytotoxicity of ambient air particles to rat lung macrophages: comparison of cellular and functional assays. Toxicol. In Vitro 10: 161-172.

Nakamura, T.; Hayashida, Y. (1992) Autonomic cardiovascular responses to smoke exposure in conscious rats. Am. J. Physiol. 262: R738-745.

National Institutes of Health. (1997) Guidelines for the diagnosis and management of asthma: expert panel report 2. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; publication no. 97-4051.

Nemmar, A.; Delaunois, A.; Nemery, B.; Dessy-Doizé, C.; Beckers, J.-F.; Sulon, J.; Gustin, P. (1999) Inflammatory effect of intratracheal instillation of ultrafine particles in the rabbit: role of C-fiber and mast cells. Toxicol. Appl. Pharmacol. 160: 250-261.

Nightingale, J. A.; Maggs, R.; Cullinan, P.; Donnelly, L. E.; Rogers, D. F.; Kinnersley, R.; Chung, K. F.; Barnes, P. J.; Ashmore, M.; Newman-Taylor, A. (2000) Airway inflammation after controlled exposure to diesel exhaust particulates. Am. J. Respir. Crit. Care Med. 162: 161-166.

Ning, Y.; Imrich, A.; Goldsmith, C. A.; Qin, G.; Kobzik, L. (2000) Alveolar macrophage cytokine production in response to air particles in vitro: role of endotoxin. J. Toxicol. Environ. Health A 59: 165-180.

Nordenhäll, C.; Pourazar, J.; Ledin, M. C.; Levin, J. O.; Sandström, T.; Ädelroth, E. (2001) Diesel exhaust enhances airway responsiveness in asthmatic subjects. Eur. Respir. J. 17: 909-915.

Norwood, J., Jr.; Ledbetter, A. D.; Doerfler, D. L.; Hatch, G. E. (2001) Residual oil fly ash inhalation in guinea pigs: influence of absorbate and glutathione depletion. Toxicol. Sci. 61: 144-153.

Oberdörster, G. (1996) Effects of ultrafine particles in the lung and potential relevance to environmental particles. In: Marijnissen, J. C. M.; Gradon, L., eds. Proceedings of Aerosol inhalation, lung transport, deposition and the relation to the environment: recent research frontiers, an international workshop; September,1995; Warsaw, Poland. London, United Kingdom: Kluwer Academic; pp. 165-174.

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

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

Oberdörster, G.; Finkelstein, J. N.; Johnston, C.; Gelein, R.; Cox, C.; Baggs, R.; Elder, A. C. P. (2000) Acute pulmonary effects of ultrafine particles in rats and mice. Cambridge, MA: Health Effects Institute; research report no. 96.

Oettinger, R.; Drumm, K.; Knorst, M.; Krinyak, P.; Smolarski, R.; Kienast, K. (1999) Production of reactive oxygen intermediates by human macrophages exposed to soot particles and asbestos fibers and increase in NF-kappa B p50/p105 mRNA. Lung 177: 343-354.

Ohtoshi, T.; Takizawa, H.; Okazaki, H.; Kawasaki, S.; Takeuchi, N.; Ohta, K.; Ito, K. (1998) Diesel exhaust particles stimulate human airway epithelial cells to produce cytokines relevant to airway inflammation in vitro. J. Allergy Clin. Immunol. 101: 778-785.

Ohtsuka, Y.; Clarke, R. W.; Mitzner, W.; Brunson, K.; Jakab, G. J.; Kleeberger, S. R. (2000a) Interstrain variation in murine susceptibility to inhaled acid-coated particles. Am. J. Physiol. L469-L476.

Ohtsuka, Y.; Brunson, K. J.; Jedlicka, A. E.; Mitzner, W.; Clarke, R. W.; Zhang, L.-Y.; Eleff, S. M.; Kleeberger, S. R. (2000b) Genetic linkage analysis of susceptibility to particle exposure in mice. Am. J. Respir. Cell Mol. Biol. 22: 574-581.

Oortgiesen, M.; Veronesi, B.; Eichenbaum, G.; Kiser, P. F.; Simon, S. A. (2000) Residual oil fly ash and charged polymers activate epithelial cells and nociceptive sensory neurons. Am. J. Physiol. 278: L683-L695.

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

Osier, M.; Baggs, R. B.; Oberdörster, G. (1997) Intratracheal instillation versus intratracheal inhalation: influence of cytokines on inflammatory response. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1265-1271.

Osman, K.; Zejda, J. E.; Schütz, A.; Mielzynska, D.; Elinder, C. G.; Vahter, M. (1998) Exposure to lead and other metals in children from Katowice district, Poland. Int. Arch. Occup. Environ. Health 71: 180-186.

Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.

Petrovic, S.; Urch, B.; Brook, J.; Datema, J.; Purdham, J.; Liu, L.; Lukic, Z.; Zimmerman, B.; Tofler, G.; Downar, E.; Corey, P.; Tarlo, S.; Broder, I.; Dales, R.; Silverman, F. (1999) Cardiorespiratory effects of concentrated ambient PM2.5: a pilot study using controlled human exposures. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 173-188.

Pierce, L. M.; Alessandrini, F.; Godleski, J. J.; Paulauskis, J. D. (1996) Vanadium-induced chemokine mRNA expression and pulmonary inflammation. Toxicol. Appl. Pharmacol. 138: 1-11.

Pinkerton, K. E.; Brody, A. R.; Miller, F. J.; Crapo, J. D. (1989) Exposure to low levels of ozone results in enhanced pulmonary retention of inhaled asbestos fibers. Am. Rev. Respir. Dis. 140: 1075-1081.

Pinto, M.; Birnbaum, S. C.; Kadar, T.; Goldberg, G. M. (1979) Lung injury in mice induced by factors acting synergistically with inhaled particulate antigen. Clin. Immunol. Immunopathol. 13: 361-368.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Prahalad, A. K.; Soukup, J. M.; Inmon, J.; Willis, R.; Ghio, A. J.; Becker, S.; Gallagher, J. E. (1999) Ambient air particles: effects on cellular oxidant radical generation in relation to particulate elemental chemistry. Toxicol. Appl. Pharmacol. 158: 81-91.

Pritchard, R. J.; Ghio, A. J.; Lehmann, J. R.; Winsett, D. W.; Tepper, J. S.; Park, P.; Gilmour, M. I.; Dreher, K. L.; Costa, D. L. (1996) Oxidant generation and lung injury after particulate air pollutant exposure increase with the concentrations of associated metals. Inhalation Toxicol. 8: 457-477.

Prows, D. R.; Shertzer, H. G.; Daly, M. J.; Sidman, C. L.; Leikauf, G. D. (1997) Genetic analysis of ozone-induced acute lung injury in sensitive and resistant strains of mice. Nat. Genet. 17: 471-474.

Prows, D. R.; Leikauf, G. D. (2001) Quantitative trait analysis of nickel-induced acute lung injury in mice. Am. J. Respir. Cell Mol. Biol. 24: 740-746.

Quay, J. L.; Reed, W.; Samet, J.; Devlin, R. B. (1998) Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-κB activation. Am. J. Respir. Cell Mol. Biol. 19: 98-106.

Rose, C. S.; Martyny, J. W.; Newman, L. S.; Milton, D. K.; King, T. E., Jr.; Beebe, J. L.; McCammon, J. B.; Hoffman, R. E.; Kreiss, K. (1998) "Lifeguard lung": endemic granulomatous pneumonitis in an indoor swimming pool. Am. J. Public Health 88: 1795-1800.

Rudell, B.; Sandström, T.; Hammarström, U.; Ledin, M.-L.; Hörstedt, P.; Stjernberg, N. (1994) Evaluation of an exposure setup for studying effects of diesel exhaust in humans. Int. Arch. Occup. Environ. Health 66: 77-83.

Rudell, B.; Ledin, M.-C.; Hammarström, U.; Stjernberg, N.; Lundbäck, B.; Sandström, T. (1996) Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. Occup. Environ. Med. 53: 658-662.

Rudell, B.; Blomberg, A.; Helleday, R.; Ledin, M.-C.; Lundbäck, B.; Stjernberg, N.; Hörstedt, P.; Sandström, T. (1999) Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. Occup. Environ. Med. 56: 527-534.

Sagai, M.; Furuyama, A.; Ichinose, T. (1996) Biological effects of diesel exhaust particles (DEP). III. Pathogenesis of asthma like symptoms in mice. Free Radical Biol. Med. 21: 199-209.

Salvi, S.; Blomberg, A.; Rudell, B.; Kelly, F.; Sandström, T.; Holgate, S. T.; Frew, A. (1999) Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am. J. Respir. Crit. Care Med. 159: 702-709.

Salvi, S. S.; Nordenhall, C.; Blomberg, A.; Rudell, B.; Pourazar, J.; Kelly, F. J.; Wilson, S.; Sandström, T.; Holgate, S. T.; Frew, A. J. (2000) Acute exposure to diesel exhaust increases IL-8 and GRO-αproduction in healthy human airways. Am. J. Respir. Crit. Care Med. 161: 550-557.

Samet, J. M.; Reed, W.; Ghio, A. J.; Devlin, R. B.; Carter, J. D.; Dailey, L. A.; Bromberg, P. A.; Madden, M. C. (1996) Induction of prostaglandin H synthase 2 in human airway epithelial cells exposed to residual oil fly ash. Toxicol. Appl. Pharmacol. 141: 159-168.

Samet, J. M.; Stonehuerner, J.; Reed, W.; Devlin, R. B.; Dailey, L. A.; Kennedy, T. P.; Bromberg, P. A.; Ghio, A. J. (1997) Disruption of protein tyrosine phosphate homeostasis in bronchial epithelial cells exposed to oil fly ash. Am. J. Physiol. 272: L426-L432.

Samet, J. M.; Graves, L. M.; Quay, J.; Dailey, L. A.; Devlin, R. B.; Ghio, A. J.; Wu, W.; Bromberg, P. A.; Reed, W. (1998) Activation of MAPKs in human bronchial epithelial cells exposed to metals. Am. J. Physiol. 275: L551-L558.

Samet, J. M.; Ghio, A. J.; Costa, D. L.; Madden, M. C. (2000) Increased expression of cyclooxygenase 2 mediates oil fly ash-induced lung injury. Exp. Lung Res. 26: 57-69.

Schlüter, T.; Berg, I.; Dörger, M.; Gercken, G. (1995) Effect of heavy metal ions on the release of reactive oxygen intermediates by bovine alveolar macrophages. Toxicology 98: 47-55.

Schwartz, J. (1994) What are people dying of on high air pollution days? Environ. Res. 64: 26-35.

Seagrave, J. C.; Nikula, K. J. (2000) Multiple modes of responses to air pollution particulate materials in A549 alveolar type II cells. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 247-260.

Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. (1995) Particulate air pollution and acute health effects. Lancet (8943): 176-178.

Shukla, A.; Timblin, C.; BeruBe, K.; Gordon, T.; McKinney, W.; Driscoll, K.; Vacek, P.; Mossman, B. T. (2000) Inhaled particulate matter causes expression of nuclear factor (NF)-κB-related genes and oxidant-dependent NF-κB activation *in vitro*. Am. J. Respir. Cell Mol. Biol. 23: 182-187.

Silbajoris, R.; Ghio, A. J.; Samet, J. M.; Jaskot, R.; Dreher, K. L.; Brighton, L. E. (2000) In vivo and in vitro correlation of pulmonary map kinase activation following metallic exposure. Inhalation Toxicol. 12: 453-468.

Sindhu, R. K.; Mautz, W. J.; Kikkawa, Y. (1998) Chronic exposure to ozone and nitric acid vapor results in increased levels of rat pulmonary putrescine. Arch. Toxicol. 72: 445-449.

Sioutas, C.; Koutrakis, P.; Burton, R. M. (1995a) A technique to expose animals to concentrated fine ambient aerosols. Environ. Health Perspect. 103: 172-177.

Sioutas, D.; Koutrakis, P.; Ferguson, S. T.; Burton, R. M. (1995b) Development and evaluation of a prototype ambient particle concentrator for inhalation exposure studies. Inhalation Toxicol. 7: 633-644.

Sioutas, C.; Kim, S.; Chang, M.; Terrell, L. L.; Gong, H., Jr. (2000) Field evaluation of a modified DataRAM MIE scattering monitor for real-time $PM_{2.5}$ mass concentration measurements. Atmos. Environ. 34: 4829-4838.

Sjögren, B. (1997) Occupational exposure to dust: inflammation and ischaemic heart disease. Occup. Environ. Med. 54: 466-469.

Smith, K. R.; Aust, A. E. (1997) Mobilization of iron from urban particulates leads to generation of reactive oxygen species *in vitro* and induction of ferritin synthesis in human lung epithelial cells. Chem. Res. Toxicol. 10: 828-834.

Smith, K. R.; Veranth, J. M.; Lighty, J. S.; Aust, A. E. (1998) Mobilization of iron from coal fly ash was dependent upon the particle size and the source of coal. Chem. Res. Toxicol. 11: 1494-1500.

Soukup, J. M.; Ghio, A. J.; Becker, S. (2000) Soluble components of Utah Valley particulate pollution alter alveolar macrophage function in vivo and in vitro. Inhalation Toxicol. 12: 401-414.

Soukup, J. M.; Becker, S. (2001) Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. Toxicol. Appl. Pharmacol. 171: 20-26.

Spengler, J. D.; Thurston, G. D. (1983) Mass and elemental composition of fine and coarse particles in six U.S. cities. J. Air Pollut. Control Assoc. 33: 1162-1171.

Steerenberg, P. A.; Dormans, J. A. M. A.; Van Doorn, C. C. M.; Middendorp, S.; Vos, J. G.; Van Loveren, H. (1999) A pollen model in the rat for testing adjuvant activity of air pollution components. Inhalation Toxicol. 11: 1109-1122.

Stringer, B.; Kobzik, L. (1996) Alveolar macrophage uptake of the environmental particulate titanium dioxide: role of surfactant components. Am. J. Respir. Cell Mol. Biol. 14: 155-160.

Stringer, B.; Kobzik, L. (1998) Environmental particulate-mediated cytokine production in lung epithelial cells (A549): role of preexisting inflammation and oxidant stress. J. Toxicol. Environ. Health Part A 55: 31-44.

Stringer, B.; Imrich, A.; Kobzik, L. (1996) Lung epithelial cell (A549) interaction with unopsonized environmental particulates: quantitation of particle-specific binding and IL-8 production. Exp. Lung Res. 22: 495-508.

Su, W.-Y.; Jaskot, R. H.; Richards, J.; Abramson, S. R.; Woessner, J. F., Jr.; Yu, W.-H.; Dreher, K. L. (2000) Induction of pulmonary matrilysin expression by combustion and ambient air particles. Am. J. Physiol. 279: L152-L160.

Su, W.-Y.; Jaskot, R. H.; Dreher, K. L. (2000b) Particulate matter induction of pulmonary gelatinase A, gelatinase B, tissue inhibitor of metalloproteinase expression. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings

of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 105-119.

Sun, G.; Crissman, K.; Norwood, J.; Richards, J.; Slade, R.; Hatch, G. E. (2001) Oxidative interactions of synthetic lung epithelial lining fluid with metal-containing particulate matter. Am. J. Physiol. 281: L807-L815.

Takano, H.; Yoshikawa, T.; Ichinose, T.; Miyabara, Y.; Imaoka, K.; Sagai, M. (1997) Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. Am. J. Respir. Crit. Care Med. 156: 36-42.

Takano, H.; Ichinose, T.; Miyabara, Y.; Shibuya, T.; Lim, H.-B.; Yoshikawa, T. Sagai, M. (1998) Inhalation of diesel exhaust enhances allergen-related eosinophil recruitment and airway hyperresponsiveness in mice. Toxicol. Appl. Pharmacol. 150: 328-337.

Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The human bone marrow response to acute air pollution caused by forest fires. Am. J. Respir. Crit. Care Med. 161: 1213-1217.

Terashima, T.; Wiggs, B.; English, D.; Hogg, J. C.; Van Eeden, S. F. (1997) Phagocytosis of small carbon particles (PM_{10}) by alveolar macrophages stimulates the release of polymorphonuclear leukocytes from bone marrow. Am. J. Respir. Crit. Care Med. 155: 1441-1447.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Timblin, C.; BeruBe, K.; Chrug, A.; Driscoll, K.; Gordon, T.; Hemenway, D.; Walsh, E.; Cummins, A. B.; Vacek, P.; Mossman, B. (1998) Ambient particulate matter causes activation of the c-*jun* kinase/stress-activated protein kinase cascade and DNA synthesis in lung epithelial cells. Cancer Res. 58: 4543-4547.

Tsien, A.; Diaz-Sanchez, D.; Ma, J.; Saxon, A. (1997) The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances IgE production by IgE-secreting EBV-transformed human B cells *in vitro*. Toxicol. Appl. Pharmacol. 142: 256-263.

Tsuchiyama, F.; Hisanaga, N.; Shibata, E.; Aoki, T.; Takagi, H.; Ando, T.; Takeuchi, Y. (1997) Pulmonary metal distribution in urban dwellers. Int. Arch. Occup. Environ. Health 70: 77-84.

Turpin, B. J. (1999) Options for characterizing organic particulate matter. Environ. Sci. Technol. 33: 76A-79A.

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1989) An acid aerosols issue paper: health effects and aerometrics. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-88-005F. Available from: NTIS, Springfield, VA; PB91-125864.

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

U.S. Environmental Protection Agency. (1996b) Ambient levels and noncancer health effects of inhaled crystalline and amorphous silica: health issue assessment [draft]. Research Triangle Park, NC: National Center for Environmental Assessment; EPA report no. EPA/600/R-95/115.

U.S. Environmental Protection Agency. (2000) Health assessment document for diesel exhaust [SAB review draft]. Washington, DC: Office of Research and Development, National Center for Environmental Assessment-Washington Office; report no. EPA/600/8-90/057E. Available: http://cfpub.epa.gov/ncea/cfm/nceahome.cfm [29 March, 2002].

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1983) Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. J. Aerosol Sci. 14: 202-205.

Van Eeden, S. F.; Tan, W. C.; Suwa, T.; Mukae, H.; Terashima, T.; Fujii, T.; Qui, D.; Vincent, R.; Hogg, J. C. (2001) Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM_{10}). Am. J. Respir. Crit. Care Med. 164: 826-830.

Van Maanen, J. M.; Borm, P. J.; Knaapen, A.; Van Herwijnen, M.; Schilderman, P. A.; Smith, K. R.; Aust, A. E.; Tomatis, M.; Fubini, B. (1999) In vitro effects of coal fly ashes: hydroxyl radical generation, iron release, and DNA damage and toxicity in rat lung epithelial cells. Inhalation Toxicol. 11: 1123-1141.

Van Zijverden, M.; Granum, B. (2000a) Adjuvant activity of particulate pollutants in different mouse models. Toxicology 152: 69-77.

Van Zijverden, M.; Van der Pijl, A.; Bol, M.; Van Pinxteren, F. A.; De Haar, C.; Penninks, A. H.; Van Loveren, H.; Pieters, R. (2000b) Diesel exhaust, carbon black, and silica particles display distinct Th1/Th2 modulating activity. Toxicol. Appl. Pharmacol. 168: 131-139.

Van Zijverden, M.; De Haar, C.; Van Beelen, A.; Van Loveren, H.; Penninks, A.; Pieters, R. (2001) Co-administration of antigen and particles optimally stimulates the immune response in an intranasal administration model in mice. Toxicol. Appl. Pharmacol. 177: 174-178.

Vanda, B.; de Buen, N.; Jasso, R.; Valero, G.; Vargas, M. H.; Olmos, R.; Arreola, J. L.; Santillán, P.; Alonso, P. (1998) Inflammatory cells and ferruginous bodies in bronchoalveolar lavage in urban dogs. Acta Cytol. 42: 939-944.

Veronesi, B.; Oortgiesen, M. (2001) Neurogenic inflammation and particulate matter (PM) air pollutants. Neurotoxicology 22: 795-810.

Veronesi, B.; Carter, J. D.; Devlin, R. B.; Simon, S. A.; Oortgiesen, M. (1999a) Neuropeptides and capsaicin stimulate the release of inflammatory cytokines in a human bronchial epithelial cell line. Neuropeptides 33: 447-456.

Veronesi, B.; Oortgiesen, M.; Carter, J. D.; Devlin, R. B. (1999b) Particulate matter initiates inflammatory cytokine release by activation of capsaicin and acid receptors in a human bronchial epithelial cell line. Toxicol. Appl. Pharmacol. 154: 106-115.

Veronesi, B.; Oortgiesen, M.; Roy, J.; Carter, J. D.; Simon, S. A.; Gavett, S. H. (2000) Vanilloid (capsaicin) receptors influence inflammatory sensitivity in response to particulate matter. Toxicol. Appl. Pharmacol. 169: 66-76.

Veronesi, B.; De Haar, C.; Roy, J.; Oortgiesen, M. (2002a) Particulate matter inflammation and receptor sensitivity are target cell specific. Inhalation Toxicol. 14: 101-125.

Veronesi, B.; De Haar, C.; Lee, L.; Oortgiesen, M. (2002b) The surface charge of particulate matter related to cytokine release in human bronchial epithelial cells (BEAS-2B). Toxicol. Appl. Pharmacol. 179: XX

Vincent, R.; Bjarnason, S. G.; Adamson, I. Y. R.; Hedgecock, C.; Kumarathasan, P.; Guénette, J.; Potvin, M.; Goegan, P.; Bouthillier, L. (1997) Acute pulmonary toxicity of urban particulate matter and ozone. Am. J. Pathol. 151: 1563-1570.

Vincent, R.; Kumarathasan, P.; Goegan, P.; Bjarnason, S. G.; Guénette, J.; Bérubé, D.; Adamson, I. Y.; Desjardins, S.; Burnett, R. T.; Miller, F. J.; Battistini, B. (2001) Inhalation toxicology of urban ambient particulate matter: acute cardiovascular effect in rats. Boston, MA: Health Effects Institute; research report no. 104. Available: http://www.healtheffects.org/Pubs/Vincent.pdf [29 January 02].

Vogelzang, P. F. J.; Van Der Gulden, J. W. J.; Folgering, H.; Kolk, J. J.; Heederik, D.; Preller, L.; Tielen, M. J. M.; Van Schayck, C. P. (1998) Endotoxin exposure as a major determinant of lung function decline in pig farmers. Am. J. Respir. Crit. Care Med. 157: 15-18.

Wagner, J. G.; Hotchkiss, J. A.; Harkema, J. R. (2001) Effects of ozone and endotoxin coexposure on rat airway epithelium: potentiation of toxicant-induced alterations. Environ. Health Perspect. 109(suppl. 4): 591-598.

Walters, D. M.; Breysse, P. N.; Wills-Karp, M. (2001) Ambient urban Baltimore particulate-induced airway hyperresponsiveness and inflammation in mice. Am. J. Respir. Crit. Care Med. 164: 1438-1443.

Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol. Sci. 41: 209-216.

Watkinson, W. P.; Campen, M. J.; Nolan, J. P.; Kodavanti, U. P.; Dreher, K. L.; Su, W.-Y.; Highfill, J. W.; Costa, D. L. (2000a) Cardiovascular effects following exposure to particulate matter in healthy and cardiopulmonary-compromised rats. In: Heinrich, U.; Mohr, U., eds. Relationships between acute and chronic effects of air pollution. Washington, DC: ISLI Press, pp. 447-463.

Watkinson, W. P.; Campen, M. J.; Dreher, K. L.; Su, W.-Y.; Kodavanti, U.P.; Highfill, J. W.; Costa, D. L. (2000b) Thermoregulatory effects following exposure to particulate matter in healthy and cardiopulmonary-compromised rats. J. Therm. Biol. 25: 131-137.

Wesselkamper, S. C.; Prows, D. R.; Biswas, P.; Willeke, K.; Bingham, E.; Leikauf, G. D. (2000) Genetic susceptibility to irritant-induced acute lung injury in mice. Am. J. Physiol. 279: L575-L582.

Wheatley, L. M.; Platts-Mills, T. A. E. (1996) Perennial allergens and the asthma epidemic. Sci. Med. 3: 6-13.

Woodin, M. A.; Hauser, R.; Liu, Y.; Smith, T. J.; Siegel, P. D.; Lewis, D. M.; Tollerud, D. J.; Christiani, D. C. (1998) Molecular markers of acute upper airway inflammation in workers exposed to fuel-oil ash. Am. J. Respir. Crit. Care Med. 158: 182-187.

Wu, W.; Samet, J. M.; Ghio, A. J.; Devlin, R. B. (2001) Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to Utah Valley PM. Am. J. Physiol. 281: L483-L489.

Zelikoff, J. T.; Sisco, M.; Cohen, M. D.; Frampton, M. W.; Utell, M. J; Schlesinger, R. B. (1994) Interspecies comparison of immunotoxicity of inhaled sulfuric acid. II. New Zealand white rabbits. In: 1994 international conference sponsored by the American Lung Association and the American Thoracic Society; May; Boston, MA. Am. J. Respir. Crit. Care Med. 149: A621.

Zelikoff, J. T.; Frampton, M. W.; Cohen, M. D.; Morrow, P. E.; Sisco, M.; Tsai, Y.; Utell, M. J.; Schlesinger, R. B. (1997) Effects of inhaled sulfuric acid aerosols on pulmonary immunocompetence: a comparative study in humans and animals. Inhalation Toxicol. 9: 731-752.

Zhang, T.; Huang, C.; Johns, E. J. (1997) Neural regulation of kidney function by the somatosensory system in normotensive and hypertensive rats. Am. J. Physiol. 273: R1749-R1757.

Zock, J.-P.; Hollander, A.; Heederik, D.; Douwes, J. (1998) Acute lung function changes and low endotoxin exposures in the potato processing industry. Am. J. Ind. Med. 33: 384-391.

8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS FROM AMBIENT PARTICULATE MATTER

8.1 INTRODUCTION

Epidemiology studies linking community ambient PM concentrations to adverse health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD), and continue to play an important role. Those studies are indicative of measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations being associated with ambient levels of $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, and other indicators of PM exposure. The numerous more recent epidemiologic studies reviewed in this chapter generally identify more cities where ambient PM-relationships with morbidity and mortality have been found and, thereby, both extend the earlier findings and provide an expanded evidence base that substantiates health effects being associated with exposures to PM at concentrations currently encountered in the United States.

The epidemiology studies presented here should be considered in combination with the ambient concentration information presented in Chapter 3, the studies of human PM exposure in Chapter 5, and the discussions of PM dosimetry and toxicology in Chapters 6 and 7. The contribution of the epidemiology studies is to evaluate associations between health effects and exposures of human populations to ambient PM and to help identify susceptible subgroups and associated risk factors. Chapter 9 provides a concise interpretive synthesis of the information.

This chapter opens with a brief overview of key general features of the several types of epidemiologic studies assessed in the chapter and a discussion of important general methodological issues that must be considered in their critical assessment. After this brief introduction, Section 8.2 assesses studies of PM effects on mortality. Section 8.3 evaluates studies of morbidity as a health endpoint. Section 8.4 then provides an interpretive assessment of the overall PM epidemiologic data base in relation to a variety of key issues and potential inferences associated with studies reviewed in Sections 8.2 and 8.3. The overall key findings and conclusions for this chapter are then summarized in Section 8.5.

8.1.1 Types of Epidemiology Studies Reviewed

Definitions of various types of epidemiology studies used here were provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are briefly summarized here. Briefly, the epidemiology studies are divided into *mortality* studies and *morbidity* studies. *Mortality* studies evaluating PM effects on total (non-accidental) mortality and cause-specific mortality have provided the most unambiguous evidence of a clearly adverse endpoint. The *morbidity* studies further substantiate PM effects on a wide range of health endpoints, such as: cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory symptoms, self-medication in asthmatics, changes in pulmonary function tests (PFT), low birthweight infants, etc.

The epidemiology strategies most commonly used in PM health studies are of four types: (1) *ecologic studies;* (2) *time-series semi-ecologic studies;* (3) *longitudinal panel and prospective cohort studies;* and (4) *case-control and crossover studies*. All of these are observational studies rather than experimental studies, since participants are not assigned at random to air pollution exposures. In general, the exposure of the participant is not directly observed, and the concentration of airborne particles and other air pollutants at one or more stationary air monitors is used as a proxy for individual exposure to ambient air pollution.

In *ecologic studies*, the responses are at a community level (for example, annual mortality rates), as are the exposure indices (for example, annual average particulate matter concentrations) and covariates (for example, the percentage of the population greater than 65 years of age). No individual data is used in the analysis, therefore the relation between health effect and exposure calculated across different communities may not reflect individual-level associations between health outcome and exposure. The use of proxy measures for individual exposure and covariates or effects modifiers may also bias the results, and within-city or within-unit confounding may be overlooked.

Time series studies are more informative because they allow study of associations between *changes* in outcomes and *changes* in exposure indicators preceding or simultaneous with the outcome. The temporal relationship supports a conclusion of a causal relation, even when both the outcome (for example, the number of non-accidental deaths in a city during a day) and the exposure (for example, daily air pollution concentration) are community indices.

1   *Prospective cohort (or panel) studies* use data from individuals, including health status

2   (where available), individual exposure (not usually available), and individual covariates or risk

3   factors, observed over time. The participants in a prospective cohort study are ideally recruited,

4   using a simple or stratified random sample so as to represent a target population for which

5   individual or community exposure of the participants is known before and during the interval up

6   to the time the health endpoint occurs. The use of individual-level data is believed to give

7   prospective cohort studies greater inferential strength than other epidemiology strategies, but the

8   use of community-level or estimated exposure data may weaken this advantage, as in time-series

9   studies.

10   *Case-control studies* are retrospective studies in that exposure is determined after the health

11   endpoint occurs (this is common in occupational health studies). As Rothman and Greenland

12   (1998) describe it, "Case-control studies are best understood by defining a source population,

13   which represents a hypothetical study population in which a cohort study might have been

14   conducted . . . In a case-control study, the cases are identified and their exposure status is

15   determined just as in a cohort study . . . [and] a control group of study subjects is sampled from

16   the entire source population that gives rise to the cases . . . the cardinal requirement of control

17   selection is that the controls must be sampled independently of their exposure status."

18   The *case-crossover design* is suited to the study of a transient effect of an intermittent

19   exposure on the subsequent risk of a rare acute-onset disease hypothesized to occur a short time

20   after exposure. In the original development of the method, effect estimates were based on

21   within-subject comparisons of exposures associated with incident disease events with exposures

22   at times before the occurrence of disease, using matched case-control methods or methods for

23   stratified follow-up studies with spare data within each stratum. The principle of the analysis is

24   that the exposures of cases just before the event are compared with the distribution of exposure

25   estimated from some separate time period. This distribution is assumed to be representative of

26   the distribution of exposures for those individuals while they are at risk of developing the

27   outcome of interest.

28   When measurements of exposure or potential effect modifiers are available on an

29   individual level, it is possible to incorporate this information into a case-crossover study unlike a

30   time-series analysis. A disadvantage of the case-crossover design, however, is the potential for

31   bias due to time trends in the exposure time-series. Since case-crossover comparisons are made

1 between different points in time, the case-crossover analysis implicitly depends on an assumption

2 that the exposure distribution is stable over time (stationary). If the exposure time-series is

3 non-stationary and case exposures are compared with referent exposures systematically selected

4 from a different period in time, a bias may be introduced into estimates of the measure of

5 association for the exposure and disease. These biases are particularly important when

6 examining the small associations that appear to exist between PM and health outcomes.

7

8.1.2 Confounding and Effect Modification

9   A pervasive problem in the analysis of epidemiology data, no matter what design or

10 strategy, is the unique attribution of the health outcome to the nominal causal agent (i.e., airborne

11 particles) in this document. The health outcomes attributed to particles are not specific (for

12 example, mortality in a broad range of ICD-9 categories) and may also be attributable to high or

13 low temperatures, influenza and other diseases, and/or exposure to gaseous criteria air pollutants.

14 Many of the other factors can be measured, directly or by proxies. Some of these co-variables

15 are *confounders*, others are *effect modifiers*. The distinctions are important.

16   *Confounding* is " . . . a confusion of effects. Specifically, the apparent effect of the

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

18 mixed with the actual exposure effect (which may be null)." (Rothman and Greenland, 1998,

19 p. 120). These authors list three criteria for a confounding factor:

20   (1) A confounding factor must be a risk factor for the disease (health effect).

21   (2) A confounding factor must be associated with the exposure under study in the source

22   population (the population at risk from which the cases are derived).

23   (3) A confounding factor must not be affected by the exposure or the disease, i.e., it cannot

24   be an intermediate step in the causal path between the exposure and the disease.

25   A causal pathway is one in which members of the population are exposed to putative causal

26 agents that can actually produce the observed health effect. The primary cause may be mediated

27 by secondary causes (possibly proximal to exposure) and may have either a direct effect on

28 exposure or an indirect effect through the secondary causes, or both, as illustrated below.

29 A non-causal pathway may involve factors that are not associated with the health effect or for

30 which there is no population exposure, so that the factors are not potential confounders.

1   The determination of whether a potential confounder is an actual confounder depends on
2   biological or physical knowledge about its exposure and health effects. Patterns of association in
3   epidemiology may be helpful in suggesting where to look for this knowledge, but do not replace
4   it. Gaseous criteria pollutants (CO, NO_2, SO_2, O_3) are candidates for confounders since: (1) all
5   of these have adverse health effects, with CO more often identified with cardiovascular effects
6   and the others with respiratory effects (including symptoms and hospital admissions), as part of
7   the wide spectrum of cardiopulmonary disease also associated with particles; (2) the gaseous
8   criteria pollutants may be associated with particles for several reasons, including (a) common
9   sources, (b) correlated changes in response to wind and weather, and (c) SO_2 and NO_2 may be
10   precursors to sulfate and nitrate components of ambient particle mixes, while NO_2 contributes to
11   the formation of organic aerosols during photochemical transformations.
12   A common source, such as combustion of gasoline in motor vehicles emitting CO, NO_2,
13   and primary particles, may play an important role in confounding among these pollutants, as does
14   weather and seasonal effects. Even though O_3 is a secondary pollutant also associated with
15   emission of NO_2, it is often less highly associated with particles. Levels of SO_2 in the western
16   U.S. are often quite low, so that secondary formation of particle sulfates plays a much smaller
17   role there, resulting in usually relatively little confounding of SO_2 with PM mass concentration in
18   the west. On the other hand, in the industrial midwest and northeastern states, SO_2 and sulfate
19   levels during many of the epidemiology studies were relatively high and highly correlated with
20   fine particle mass concentrations, so that criterion 3 (no causal path leading from confounder to
21   exposure, or exposure to confounder to health effect) may not be strictly true for SO_2 vs sulfate
22   or overall fine particle mass. If the correlation with PM and SO_2 is not too high, it may be
23   possible to estimate some part of their independent effects. If there is a causal pathway, then it is
24   not clear whether the observed relation of exposure to health effect is a direct effect of the
25   exposure, an indirect effect mediated by the confounder, or a mixture of these.
26   Most extraneous variables fall into the category of *effect modifiers*. "Effect-measure
27   modification differs from confounding in several ways. The main difference is that, whereas
28   confounding is a bias that the investigator hopes to prevent or remove from the effect estimate,
29   effect-measure modification is a property of the effect under study . . . In epidemiologic analysis
30   one tries to eliminate confounding but one tries to detect and estimate effect-measure
31   modification." (Rothman and Greenland, 1998, p. 254). Examples of effect modifiers in some

1   of the studies evaluated in this chapter include environmental variables (such as temperature or

2   humidity in time-series studies), individual risk factors (such as education, cigarette smoking

3   status, age in a prospective cohort study), and community factors (such as percent of population

4   > 65 years old). It is often possible to stratify the relationship between health outcome and

5   exposure by one or more of these risk factor variables.

6   Effect modifiers may be encountered within a single-city time series studies, or across cities

7   in a two-stage hierarchical model or meta-analysis. We will use the latter case to illustrate some

8   of the possibilities using a hypothetical case with four cities in which a co-pollutant of the PM

9   index is to be evaluated as a possible effect modifier. In the examples in Figure 8-1, we assume

10   that the co-pollutant has a relatively high positive correlation with the PM index. It is also

11   assumed that the excess relative risk for PM is calculated in a model in which PM is the only air

12   pollutant. For any given co-pollutant concentration within each city, there is likely to be only a

13   modest range of values of the PM index and the associated excess relative risk, as is suggested by

14   the elliptical figures. The relationship between mortality and PM in Figure 8-1a is assumed to be

15   the same and positive in all four cities; thus, with increasing co-pollutant concentration within

16   each city, the excess relative risk increases because the co-pollutant is strongly correlated with

17   the PM index. However, in the hypothetical 8-1a, the co-pollutant is not an effect modifier for

18   PM, as can be shown by a regression of the estimated mean PM effect on the mean co-pollutant

19   concentration across the four cities.

20   The relationship between PM and mortality in Figure 8-1b is assumed to differ across the

21   four cities, ranging from strongly negative in City 1 to strongly positive in City 4. Thus, with

22   increasing co-pollutant concentration within each city, the excess relative risk decreases in City 1

23   and City 2 but increases in City 3 and City 4, because the co-pollutant is strongly correlated with

24   the PM index. In the hypothetical Figure 8-1b, the co-pollutant is an effect modifier for PM, as

25   can be shown by a regression of the estimated mean PM effect on the mean co-pollutant

26   concentration across the four cities, even though the simple mean of the excess relative risks

27   across the four cities is nearly zero. A relationship would be found if all within-city effects were

28   positive, or if the across-city ecological regression were negative. Stratification by levels of the

29   putative effect modifier is also often useful.

30   Potential confounding (Figure 8-2a) is more difficult to identify and several statistical

31   methods are available, none of them being completely satisfactory. The ususal methods are:
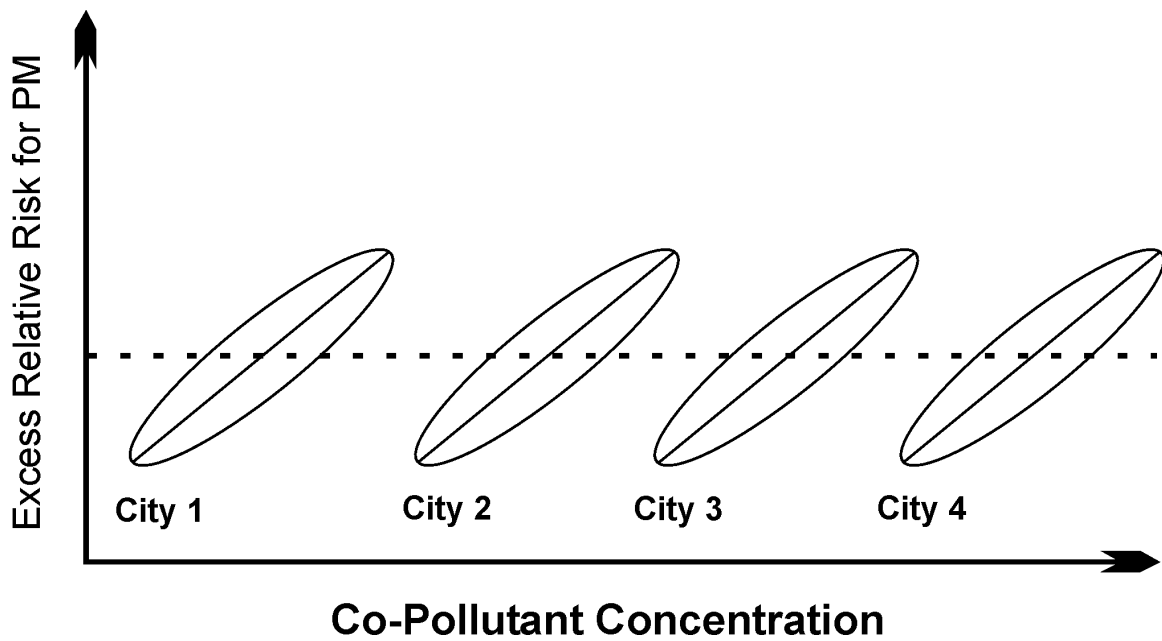
Figure 8-1a. **Strong within-city association between PM and mortality, but no second-stage association.**
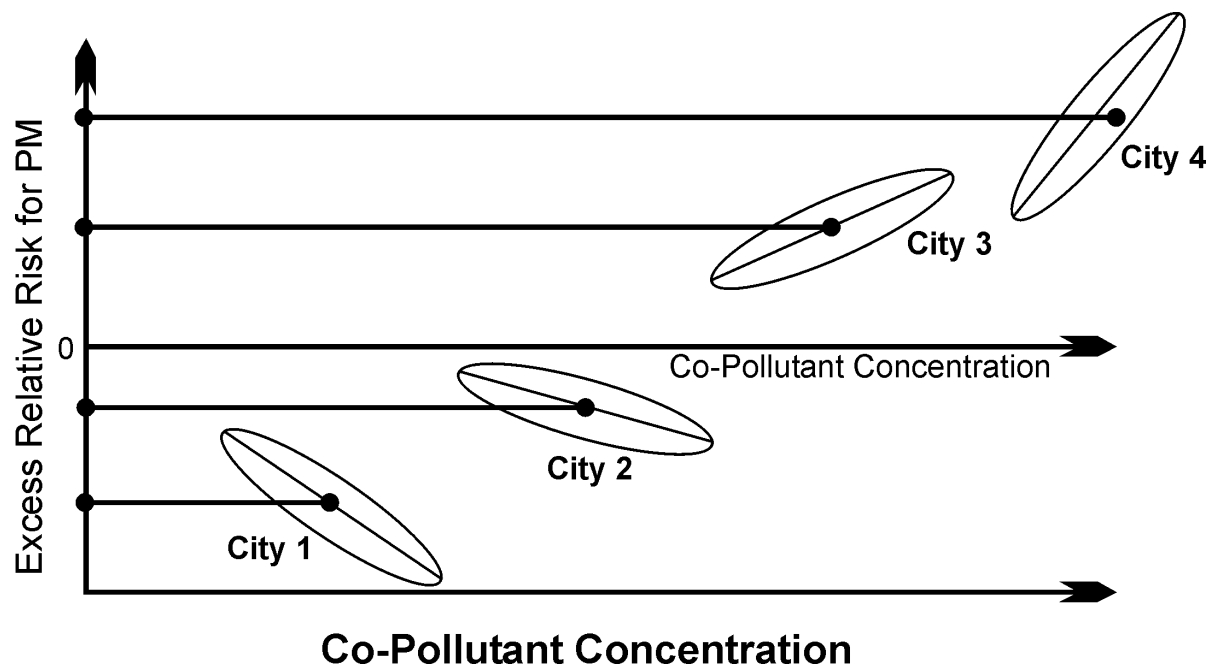
Figure 8-1b. **Within-city association between PM and mortality ranges from negative to positive with mean across cities approximately zero, but with strong positive second-stage association.**
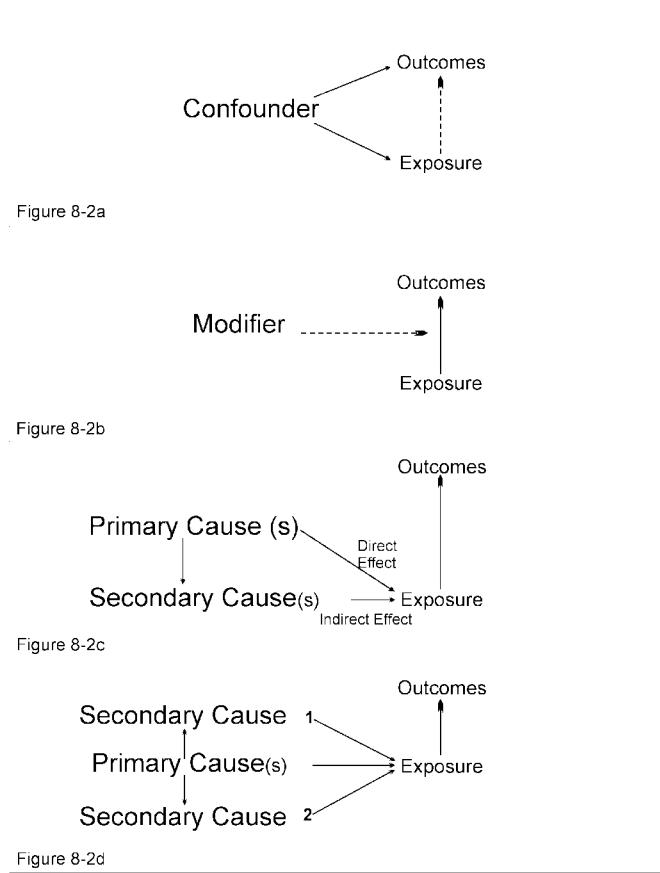
Figure 8-2. **(a) Graphical depiction of confounding; (b) Graphical depiction of effect modification; (c) Graphical depiction of a causal agent with a secondary confounder; (d) Graphical depiction of a causal agent and two potential confounders.**

1   *Within a city:*

2   (A)   Fit both a single-pollutant model and then several multi-pollutants models, and

3   determine if including the co-pollutants greatly changes the estimated effect and

4   inflates its estimated standard error;

5   (B)   If the PM index and its co-pollutants are nearly multi-collinear, carry out a factor

6   analysis, and determine which gaseous pollutants are most closely associated with

7   PM in one or more common factors.

8

9

1		*Using data from several cities:*
2	(C)	Proceed as in Method A and pool the effect size estimates across cities for single-
3		and multi-pollutant models;
4	(D)	Carry out a hierarchical regression of the PM effects vs. the mean co-pollutant
5		concentration and determine if there is a significant relationship;
6	(E)	First carry out a regression of PM vs. the co-pollutant concentration within each city
7		and the regression coefficient of mortality vs. PM for each city. Then fit a second-
8		stage model regressing the mortality-PM coefficient vs. the PM-co-pollutant
9		coefficient, concluding that the co-pollutant is a confounder if there is a significant
10		regression coefficient at the second stage (See Figure 8-2c).

11   The disadvantages of the methods are discussed in detail in Section 8.4. Briefly, the multi-

12   pollutant regression coefficients in method A may be unstable and have greatly inflated standard

13   errors, weakening their interpretation. In method B, the factors may be sensitive to the choice of

14   co-pollutants and the analysis method, and may be difficult to relate to real-world entities.

15   In method C, as with any meta-analysis, it is necessary to consider the heterogeneity of the

16   within-city effects before pooling them. Several large multi-city studies have revealed

17   unexpected heterogeneity, not fully explained at present.

18   While method D is sometimes interpreted as showing confounding if the regression

19   coefficient is non-zero, this is an argument for effect modification, not confounding.

20   Method E is sensitive to the assumptions being made. For example, if PM is the primary

21   cause in Figure 8-2c and the co-pollutant the secondary cause, then the two-stage approach may

22   be valid. However, if the model is mis-specified and there are two or more secondary causes,

23   some of which may not be identified, then the method may give misleading results.

24   An additional issue of great relevance is whether or not the population in a community time

25   series study or the participants in a prospective cohort study are exposed to measurable levels of

26   the potential confounder, particularly the ambient gaseous co-pollutants. If there is no exposure,

27   then the potential confounder does not satisfy the requirement that it is related to both exposure

28   and outcomes. This is discussed in Section 8.4 in connection with the role of exposure

29   measurement errors in air pollution epidemiology.

30

31

8.1.3 Selection of Studies for Review and Ambient PM Increments Used to Report Risk Estimates

Numerous PM epidemiology papers have been published since the 1996 PM AQCD. An ongoing medline search has been and is continuing to be conducted in conjunction with other strategies to identify PM literature pertinent to developing criteria for PM NAAQS. Those epidemiologic studies that relate measures of ambient PM to human health outcomes are assessed in this chapter, but occupational exposures studies are not. Some of the criteria used for selecting relevant literature for consideration here include whether a given study presents: (1) pertinent ambient PM indices: e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, etc.; (2) analyses of health effects of specific PM chemical or physical constituents (e.g., metals, sulfates, nitrates or ultrafine particles, etc.); (3) health endpoints not previously extensively researched; (4) multiple pollutant analyses; and/or (5) for long-term effects, mortality displacement information. The publication of pertinent new studies has been and is proceeding at a prodigious rate; and the review and evaluation of pertinent literature in this PM AQCD development process is an ongoing process which continues to obtain and assess new evidence.

The literature review method is similar to those used by others (e.g., Basu and Samet, 2000): (a) Establish a publication base using Medline and other data bases using a set of key words (particles, air pollution, mortality, morbidity, cause of death, PM, and others); (b) add papers to the publication base by staff review of Current Contents and tables of contents of journals in which relevant papers are published; and (c) staff requests to scientists known to be active in this field for papers recently accepted for publication. Efforts have been made to assess here pertinent new studies published mainly through December, 2001, as well as some studies published in early 2002 as acquired (if, in the opinion of staff, such recent new papers provide important inputs towards resolving critical scientific uncertainties).

The effect of mortality from exposure to PM or other pollutants in this document is usually expressed as a relative risk or risk rate (RR) relative to a baseline mortality or morbidity rate. The crude mortality rates in 88 cities in 48 contiguous states in the NMMAPS study ranged from about 8 deaths per day per million population in Denver, CO to about 40 per day per million in St. Petersburg, FL. It is likely that age-adjusted rates such as those used in the APHEA 2 study (Katsouyanni et al., 2001) would have shown a smaller range. As reported in Samet et al. (2000a), there was little association between PM_{10} effect size and crude mortality rate in the

1 continental U.S. cites; however, Katsouyanni et al. (2001) found a negative relation between

2 PM_{10}-equivalent effect size estimates and age-adjusted mortality rate in 29 European cities.

3 We plotted the relationship between increased or decreased mortality rate in NMMAPS for

4 ranges between the 25th and 75 percentiles (results not shown), but there was little apparent new

5 information in those plots other than the RR.

6   The PM increments used in this document to convert regression coefficients into

7 meaningful increments of excess risk are based on data from the U.S. fine particle monitoring

8 network for 1999 and 2000, the most recent years available. The difference between the annual

9 mean and the annual 95th percentile was used to characterize annual variation within each site;

10 and the average across all sites was used to select an appropriate increment for short-term

11 studies, about 50 μg/m^3 for PM_{10} and 25 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$, after rounding for ease of

12 calculation. As there is little experimental evidence about differences in effects of fine ($PM_{2.5}$)

13 and coarse ($PM_{10-2.5}$) particles, common increments are used for both. The difference between the

14 average of annual mean PM concentrations across all sites and the average of the annual 95th

15 percentiles across all sites was about 20 μg/m^3 for PM_{10} and 10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$,

16 which are values used here for PM increments in long-term studies.

17   Thus, the pollutant increments utilized here to report Relative Risks (RR's) or Odds Ratio

18 for various health effects are: for PM_{10}, 50 μg/m^3; for $PM_{2.5}$, 25 μg/m^3; for $SO_4^=$, 155 nmoles/m^3

19 (15 μg/m^3); and, for H$^+$, 75 nmoles/m^3 (3.6 μg/m^3, if as H_2SO_4) for short-term ($\leq$24 h) exposure

20 studies. The increments for short-term studies are the same as used in the 1996 PM AQCD,

21 a choice now driven by current data. In the 1996 PM AQCD, the same increments were used for

22 the long- and short-term exposure studies. However, 20 μg/m^3 is the increment used here for

23 PM_{10} and 10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$ for long-term exposure studies. These estimates

24 derived from new 1999-2000 data are smaller than these used for long-term studies in the 1996

25 PM AQCD.

26   Greater emphasis is placed in text discussions on integrating and interpreting findings from

27 the body of evidence provided by the newer studies (as well as relating them to those reviewed in

28 the 1999 PM AQCD), rather than detailed evaluation of each of the numerous newly available

29 studies. Particular emphasis is focused in the text on those studies and analyses thought to

30 provide the most pertinent information for U.S. standard setting purposes. For example, North

31 American studies conducted in the U.S. or Canada are generally accorded more text discussion

1 than those from other geographic regions; and analyses using gravimetric (mass) measurements

2 are generally accorded more text attention than those using non-gravimetric ambient PM

3 measures, e.g., black smoke (BS) or coefficient of haze (COH). Also, more emphasis is placed

4 on text discussion of new multi-city studies that employ standardized methodological analyses

5 for evaluating PM effects across several or numerous cities and often provide overall effects

6 estimates based on combined analyses of information pooled across multiple cities.

7   In the sections that follow on PM mortality and morbidity effects, key points derived from

8 the 1996 PM AQCD assessment of then-available information are first concisely highlighted.

9 Succinct summary tables are included and key information is discussed below in the main text

10 with regard to the most important numerous new studies that have become available since that

11 prior PM AQCD. More detailed information for these and other newly available studies is

12 summarized in tabular form in Appendices 8A and 8B, in which important methodological

13 features and results are presented. The Appendix tables have a uniform general organization

14 with divisions that include: (1) information about study location and ambient PM levels,

15 (2) study description of methods employed, (3) results and comments and (4) quantitative

16 outcomes for PM measures.

17

18

19 **8.2 MORTALITY EFFECTS OF PARTICULATE MATTER EXPOSURE**

20 **8.2.1 Introduction**

21   The relationship of PM and other air pollutants to excess mortality has been intensively

22 studied and has been an important issue addressed in previous PM criteria assessments (U.S.

23 Environmental Protection Agency, 1986, 1996a). Mortality is the most severe adverse health

24 endpoint and, in some ways, the easiest to study. Excellent death records are maintained at every

25 level of government in most all nations and are typically made available to researchers. Also,

26 from a narrowly technical point of view, individual deaths are more amenable to statistical

27 analyses, since individual deaths from natural causes (typically respiratory and cardiovascular

28 diagnoses) are statistically independent, except in rare extremely infectious instances. Individual

29 deaths are also non-recurring events, unlike hospital admissions or respiratory symptoms.

30

1   Recent findings are evaluated here for the two most important epidemiology designs by

2   which mortality is studied: time-series mortality studies (Section 8.2.2) and prospective cohort

3   studies (Section 8.2.3). The time-series studies mostly assess acute responses to short-term PM

4   exposure, although some recent work suggests that time-series data sets are also useful to

5   examine responses to exposures over a longer time scale. Time-series studies use community-

6   level air pollution measurements to index exposure and community-level response (i.e., the total

7   number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully

8   complement time-series studies; they use individual health records, with survival lifetimes or

9   hazard rates adjusted for individual risk factors, and typically evaluate human health impacts of

10   long-term PM exposures indexed by community-level measurements.

11

8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

14   The time-series mortality studies reviewed in the 1996 and other past PM AQCD's

15   provided much evidence that ambient PM air pollution is associated with increases in daily

16   mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published

17   between 1988 and 1996. Information derived from those studies was consistent with the

18   hypothesis that PM is a causal agent in the short-term mortality impacts of air pollution.

19   The PM_{10} relative risk estimates derived from short-term PM_{10} exposure studies reviewed

20   in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is

21   most clearly associated with an increased risk of premature total nonaccidental mortality (total

22   deaths minus those from accident/injury) on the order of relative risk (RR) = 1.025 to 1.05 in the

23   general population or, in other words, 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increase.

24   Higher relative risks were indicated for the elderly and for those with pre-existing

25   cardiopulmonary conditions. Also, based on the then recently published Schwartz et al. (1996a)

26   analysis of Harvard Six City data, the 1996 PM AQCD found the RR for excess total mortality in

27   relation to 24-h fine particle concentrations to be in the range of RR = 1.026 to 1.055 per

28   25 $\mu g/m^3$ $PM_{2.5}$ (i.e., 2.6 to 5.5% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$ increment).

29   While numerous studies reported PM-mortality associations, important issues needed to be

30   addressed in interpreting their findings. The 1996 PM AQCD extensively discussed most critical

31   issues, including: (1) seasonal confounding and effect modification; (2) confounding by weather;

1   (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold;

2   (6) harvesting and life shortening; and (7) the role of PM components. As important issues

3   related to model specification became further clarified, more studies began to address the most

4   critical issues, with some having been at least partially resolved, whereas others required still

5   further investigation. The next several paragraphs summarize the status of these issues at the

6   1996 PM AQCD publication time.

7   One of the most important components in time-series model specification is adjustment for

8   seasonal cycles and other longer-term temporal trends. Residual over-dispersion and

9   autocorrelation result from inadequate control for these temporal trends, and not adequately

10   adjusting for them could result in biased RRs. Modern smoothing methods allow efficient fits of

11   temporal trends and minimize such statistical problems. Thus, most recent studies controlled for

12   seasonal and other temporal trends, and it was unlikely that inadequate control for such trends

13   seriously biased estimated PM coefficients. Effect modification by season was examined in

14   several studies. Season-specific analyses are often not feasible in small-sized studies (due to

15   marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar

16   and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season.

17   It was not fully resolved, however, if these results represent real seasonal effect modifications or

18   may be due to varying extent of correlation between PM and co-pollutants or weather variables

19   by season.

20   While most available studies included control for weather variables, some reported

21   sensitivity of PM coefficients to weather model specification, leading some investigators to

22   speculate that inadequate weather model specifications may still have erroneously ascribed

23   residual weather effects to PM. Two PM studies (Samet et al., 1996, 1998; Pope and Kalkstein,

24   1996) involved collaboration with a meteorologist and utilized more elaborate weather modeling,

25   e.g., use of synoptic weather categories. These studies found that estimated PM effects were

26   essentially unaffected by the synoptic weather variables and also indicated that the synoptic

27   weather model did not provide better model fits in predicting mortality when compared to other

28   weather model specifications used in previous PM-mortality studies. Thus, these results

29   suggested that the reported PM effects were not explained by weather effects.

30   Many earlier PM studies considered at least one co-pollutant in the mortality regression,

31   and some also examined several co-pollutants. In most cases, when PM indices were significant

1   in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat,

2   but did not eliminate the PM associations. When multiple pollutant models were performed by

3   season, the PM coefficients became less stable, again, possibly due to PM's varying correlation

4   with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM

5   indices showed the highest significance (versus gaseous co-pollutants) in single and multiple

6   pollutant models. Thus, it was concluded that PM-mortality associations were not seriously

7   distorted by co-pollutants, but interpretation of the relative significance of each pollutant in

8   mortality regression as relative causal strength was difficult because of limited quantitative

9   information on relative exposure measurement/characterization errors among air pollutants.

10   Measurement error can influence the size and significance of air pollution coefficients in

11   time-series regression analyses and is also important in assessing confounding among multiple

12   pollutants, as varying the extent of such error among the pollutants could also influence the

13   corresponding relative significance. The 1996 PM AQCD discussed several types of such

14   exposure measurement or characterization errors, including site-to-site variability and site-to-

15   person variability—errors thought to bias the estimated PM coefficients downward in most cases.

16   However, there was not sufficient quantitative information available to estimate such bias.

17   The 1996 PM AQCD also reviewed evidence for threshold and various other functional

18   forms of short-term PM mortality associations. Several studies indicated that associations were

19   seen monotonically below the existing PM standards. It was considered difficult, however, to

20   statistically identify a threshold from available data because of low data density at lower ambient

21   PM concentrations, potential influence of measurement error, and adjustments for other

22   covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models

23   was considered adequate and appropriate.

24   The extent of prematurity of death (i.e., mortality displacement, or harvesting) in observed

25   PM-mortality associations has important public health policy implications. At the time of the

26   1996 PM AQCD review, only a few studies had investigated this issue. While one of the studies

27   suggested that the extent of such prematurity might be only a few days, this may not be

28   generalizable because this estimate was obtained for identifiable PM episodes. There was not

29   sufficient evidence to suggest the extent of prematurity for non-episodic periods, from which

30   most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

1   "In summary, most available epidemiologic evidence suggests that increased mortality

2   results from both short-term and long-term ambient PM exposure. Limitations of available

3   evidence prevent quantification of years of life lost to such mortality in the population. Life

4   shortening, lag time, and latent period of PM-mediated mortality are almost certainly

5   distributed over long time periods, although these temporal distributions have not been

6   characterized." (p. 13-45)

7   Only a limited number of PM-mortality studies analyzed fine particles and chemically

8   specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed

9   size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and

10   H^+). The results suggested that $PM_{2.5}$ was most significantly associated with mortality among the

11   components of PM. While H^+ was not significantly associated with mortality in this and an

12   earlier analysis (Dockery et al., 1992), the smaller sample size for H^+ than for other PM

13   components made a direct comparison difficult. The 1996 PM AQCD also noted that mortality

14   associations with BS or COH reported in earlier studies in Europe and the U.S. during the 1950s

15   to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50%

16   cut-off diameters ($\approx 4.5\mu m$). Furthermore, certain respiratory morbidity studies showed

17   associations between hospital admissions/visits with components of PM in the fine particle

18   range. Thus, the U.S. EPA 1996 PM AQCD concluded that there was adequate evidence to

19   suggest that fine particles play especially important roles in observed PM mortality effects.

20   Overall, then, the status of key issues raised in the 1996 PM AQCD can be summarized as

21   follows: (1) the observed PM effects are unlikely to be seriously biased by inadequate statistical

22   modeling (e.g., control for seasonality); (2) the observed PM effects are unlikely to be

23   significantly confounded by weather; (3) the observed PM effects may be to some extent

24   confounded or modified by co-pollutants, and such extent may vary from season to season;

25   (4) determining the extent of confounding and effect modification by co-pollutants requires

26   knowledge of relative exposure measurement characterization error among pollutants (there was

27   not sufficient information on this); (5) no clear evidence for any threshold for PM-mortality

28   associations was reported (statistically identifying a threshold from existing data was also

29   considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of

30   life-shortening, was reported for episodic periods (no study was conducted to investigate

31   harvesting in non-episodic U.S. data); (7) only a relatively limited number of studies suggested a

1   causal role of fine particles in PM-mortality associations, but in the light of historical data,

2   biological plausibility, and the results from morbidity studies, a greater role for fine particles than

3   coarse particles was suggested in the 1996 PM AQCD as being likely. The AQCD concluded:

4   "The evidence for PM-related effects from epidemiologic studies is fairly strong, with most

5   studies showing increases in mortality, hospital admissions, respiratory symptoms, and

6   pulmonary function decrements associated with several PM indices. These epidemiologic

7   findings cannot be wholly attributed to inappropriate or incorrect statistical methods,

8   misspecification of concentration-effect models, biases in study design or implementation,

9   measurement of errors in health endpoint, pollution exposure, weather, or other variables,

10   nor confounding of PM effects with effects of other factors. While the results of the

11   epidemiology studies should be interpreted cautiously, they nonetheless provide ample

12   reason to be concerned that there are detectable human health effects attributable to PM at

13   levels below the current NAAQS." (p. 13-92)

14

15   **8.2.2.2 Introduction to Newly Available Information on Short-Term Mortality Effects**

16   Since the 1996 PM AQCD, numerous new studies have examined short-term associations

17   between PM indices and mortality. Newly available U.S. and Canadian studies on relationships

18   between short-term PM exposure and daily mortality are summarized in Table 8-1. More

19   detailed summaries of these and of other short-term exposure PM-mortality studies from other

20   geographic areas (e.g., Europe, Asia, etc) are described in Appendix Table 8A-1. Information on

21   study location, study period, levels of PM, outcomes, methods, results, and reported risk

22   estimates and lags is provided in Table 8A-1. In addition to these summary tables, discussion in

23   the text below highlights findings from several multi-city studies. Discussion of implications of

24   new study results for types of issues identified in foregoing text is mainly deferred to Section 8.4.

25   The summarization of studies in Table 8-1 and 8A-1 (and in other tables) is not meant to

26   imply that all listed studies should be accorded equal weight in the overall interpretive

27   assessment of evidence regarding PM-associated health effects. In general, increasing scientific

28   weight should be accorded to those studies (i.e., those not clearly flawed and which have

29   adequate control for confounding) in proportion to the precision of their estimate of a health

30   effect. Small studies and studies with an inadequate exposure gradient generally produce less

31   precise estimates than large studies with an adequate exposure gradient. Therefore, the range of

32   exposures (e.g., as indicated by the IQR), the size of the study as indexed by the total number of

TABLE 8-1. RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY[*]

Reference	Location(s)	Pollutants in Models	Comments
Multi-City Mortality Studies in the U.S. and Canada			
PM$_{10}$ studies using NMMAPS data			
Samet et al. (2000a,b,c); Dominici et al. (2000a,b); Samet (2000)	88 cities in the 48 contiguous U.S. states plus AK and HI, 1987-1994; mainly 20 largest.	PM$_{10}$, O$_3$, CO, NO$_2$, SO$_2$	Numerous models; range of PM$_{10}$ values depending on city, region, co-pollutants. Pooled estimates for 88 cities, individual estimates for 20 largest with co-pollutant models
Daniels et al. (2000)	20 cities in the 48 contiguous U.S. states, 1987-1994	PM$_{10}$ only	Smooth non-parametric spline model for concentration-response functions. Average response curve nearly linear.
Dominici et al. (2002)	88 cities in the 48 contiguous U.S. states, 1987-1994	PM$_{10}$ only	Smooth non-parametric spline models for PM$_{10}$ concentration-response functions. Average response curves are nearly linear in the industrial Midwest and Northeast regions, and overall, but non-linear (usually concave) in the other regions. Possible thresholds in Southwest, Southeast.
Braga et al. (2000)	Five large U.S. cities: Chicago, IL; Detroit, MI; Pittsburgh PA, Minneapolis-St. Paul, MN; Seattle, WA	PM$_{10}$ only	Pooled estimate across cities adjusted for influenza epidemics.

[*]Brief summary of new time-series studies on daily mortality since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1969a). More complete descriptive summaries are provided in Appendix Table 8A-1. The endpoint is total daily non-trauma mortality unless noted otherwise. Due to the large number of models reported for sensitivity analyses for some of these papers, some evaluating various lags and co-pollutant models, some for individual cities and others for estimates pooled across cities, quantitative risk estimates are not presented in this table. Specific mortality risk estimates for fine and coarse particle models are shown in Table 8-2. Multiple-pollutant models are discussed in Section 8.4.2.2.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY**

Reference	Location(s)	Pollutants in Models	Comments
Multi-City Mortality Studies in the U.S. and Canada (cont'd)			
Studies using everyday PM$_{10}$ data			
Schwartz (2000b)	Same ten U.S. cities as in (Schwartz, 2000a)	PM$_{10}$ only.	Several pooled estimates across cities evaluated for single day, moving average, and distributed lags.
Schwartz and Zanobetti (2000)	Same ten U.S. cities as in (Schwartz, 2000a)	PM$_{10}$ only.	Pooled estimates of concentration-response functions across cities using smooth semi-parametric functions of PM$_{10}$ with the same span of 0.
Zanobetti and Schwartz (2000)	Four large U.S. cities: Chicago, IL; Detroit, MI, Minneapolis-St. Paul, MN; Pittsburgh, PA	PM$_{10}$ only.	Pooled estimate of effect size across cities was modified somewhat by race and gender.
Moolgavkar (2000a)	Three large U.S. counties (cities): Cook City (Chicago), IL; Los Angeles, CA; Maricopa Cty. (Phoenix), AZ.	PM$_{10}$ in all three; PM$_{2.5}$ in Los Angeles. O$_3$, CO, NO$_2$, and SO$_2$ in some models.	The results showed little consistency for different time lags and cities, the PM$_{10}$ or PM$_{2.5}$ effects on CVD mortality were greatly attenuated by including one or more gaseous co-pollutants
Pope et al. (1999a)	Ogden, Provo-Orem, and Salt Lake City, UT.	PM$_{10}$ only in all three.	Positive, significant and similar effects for PM$_{10}$ on total, CVD, and respiratory mortality
Laden et al. (2000)	Same six cities as in Harvard Six city study, with Harvard air monitors and community daily mortality time series: Boston (Watertown), MA, Harriman-Kingston, TN; Portage-Madison, WI; St. Louis, MO; Steubenville, OH; Topeka, KS.	Chemically speciated PM$_{2.5}$, and factors aligned with putative sources for each city identified by specific chemical elements as tracers.	Different coefficients in different cities, depending on source type, chemical indicators, and principal factor method. The motor vehicle combustion component was significant, other factors occasionally, but not the crustal element component.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY

Reference	Location(s)	Pollutants in Models	Comments
Multi-City Mortality Studies in the U.S. and Canada			
Tsai et al. (1999, 2000)	Camden, Elizabeth, and Newark, NJ.	$PM_{2.5}$, PM_{15}, sulfates.	Significant effects of $PM_{2.5}$, PM_{10}, and sulfates in Newark, Camden at most lags, but not Elizabeth.
Clyde et al. (2000)	Phoenix, AZ, May, 1995-March, 1998. Seattle, WA, 1990-1995.	$PM_{2.5}$, $PM_{10-2.5}$ in Phoenix. PM_{10}, $PM_{2.5}$, nephelometer, SO_2 in Seattle.	$PM_{10-2.5}$ significant in most of the 25 "best" models for Phoenix, $PM_{2.5}$ in almost none. $PM_{2.5}$ and PM_{10} in some models for Seattle, none in the 5 best.
Burnett et al. (2000)	Eight Canadian cities: Montreal, Ottawa, Toronto, Windsor, Calgary, Edmonton, Winnipeg, Vancouver	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4, O_3, CO, NO_2, SO_2	Significant effects of $PM_{2.5}$ and PM_{10}, less so for $PM_{10-2.5}$; particle effects stable, co-pollutant effects decreased by particles
Burnett et al. (1998a)	Eleven Canadian cities. 1980-1991.	Main emphasis on O_3, CO, NO_2, SO_2. $PM_{2.5}$, $PM_{10-2.5}$, SO_4 on varying schedules.	Qualitative indication of effect modification of gaseous pollutant effects by particles.
Klemm et al. (2000)	Same six cities as (Laden et al., 2000) 1979-1988.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4	Replicated Schwartz et al. (1996a) with additional sensitivity analyses.
Schwartz et al. (2002)	Same six cities as (Laden et al., 2000) 1979-1988	$PM_{2.5}$, $PM_{10-2.5}$, 15 elements in $PM_{2.5}$, O_3, CO, NO_2, SO_2	Five source factors identified, as in (Laden et al., 2000). Meta-smoothing of non-parametric concentration-mortality curves for $PM_{2.5}$ and for five source factors. Total and "traffic" source $PM_{2.5}$ significantly associated with mortality, nearly linear for $PM_{2.5}$, steeper slope at low concentrations of traffic particles. No apparent threshold.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY**

Reference	Location(s)	Pollutants in Models	Comments
Single-City Mortality Studies in the U.S. and Canada			
Ostro et al. (1999a, 2000)	Coachella Valley (Palm Springs), CA	PM_{10} in earlier study, $PM_{2.5}$ and $PM_{10-2.5}$ in later study; O_3, CO, NO_2	$PM_{2.5}$ effects significant, PM_{10} and $PM_{10-2.5}$ effects non-significant for total mortality; for cardiovascular mortality, PM_{10} and $PM_{10-2.5}$ significant, $PM_{2.5}$ not
Fairley (1999)	Santa Clara County (San Jose), CA	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, O_3, CO, NO_2.	All significant in one-pollutant models, nitrates significant in all multi-pollutant models, $PM_{2.5}$ significant except with particle nitrates.
Schwartz et al. (1999)	Spokane, WA	PM_{10} only	No association between mortality and high PM_{10} concentrations on dust storm days with high crustal particles.
Schwartz and Zanobetti (2000)	Chicago, IL	PM_{10} only	Larger effects with longer-term PM_{10} and mortality moving averages for total, in-hospital, and out-of-hospital mortality.
Lippmann et al. (2000)	Detroit, MI	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, TSP, O_3, CO, NO_2, SO_2	Positive but non-significant effects on mortality for the 1992-1994 data, but significant effects for respiratory mortality vs. PM_{10} or TSP in 1985-1990 data.
Chock et al. (2000)	Pittsburgh, PA	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, NO_2, SO_2	Fine and coarse particle data on about 1/3 of days with PM_{10}. Data split into ages < 75 and 75+, and seasons. Significant effects for PM_{10}, not for size fractions. Regional sulfate, traffic-related PM, and biogenic combustion factors have maximum associations on different lag days.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY**

Reference	Location(s)	Pollutants in Models	Comments
Single-City Mortality Studies in the U.S. and Canada			
Klemm and Mason (2000)	Atlanta, GA	$PM_{2.5}$, $PM_{10-2.5}$, nitrate, oxygenated hydrocarbons (HC), elemental carbon (EC), organic carbon (OC)	No significant effects due to short time series, ca. one year. Larger effect and shorter confidence interval for $PM_{2.5}$ than for $PM_{10-2.5}$.
Gwynn et al. (2000)	Buffalo, NY	PM_{10}, CoH, H+, SO_4, O_3, CO, NO_2, SO_2.	All PM components significantly associated with total mortality in single-pollutant models, not gaseous pollutants.
Schwartz (2000c)	Boston, MA	$PM_{2.5}$	Larger effects with longer-term $PM_{2.5}$ and mortality moving averages (span 15 to 60 days) for total and cause-specific mortality.
Lipfert et al. (2000a)	Philadelphia, PA-Camden, NJ seven-county area	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acids, metals, O_3, CO, NO_2, SO_2.	Exploration of mortality in different areas relative to air monitor location. Peak O_3 very significant, greatly reduces PM effects.
Levy (1998)	King County (Seattle), WA	PM_1 (nephelometer), PM_{10}, CO, SO_2.	PM_1 associated only with out-of-hospital ischemic heart disease deaths, total mortality with neither PM_{10} nor PM_1
Mar et al. (2000)	Phoenix, AZ, near the EPA platform monitor.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, fine particle elements, estimated soil and non-soil PM, EC, OC, O_3, CO, NO_2, SO_2; sources by factor scores.	Total mortality significantly associated with NO_2, CO, weakly with PM_{10}, $PM_{10-2.5}$, EC, SO_2. Cardiovascular mortality significantly associated with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, CO, NO_2, SO_2, source factors.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY

Reference	Location(s)	Pollutants in Models	Comments
Single-City Mortality Studies in the U.S. and Canada			
Clyde et al. (2000)	Phoenix, AZ	PM_{10}, $PM_{2.5}$	Effect on elderly mortality consistently higher for $PM_{10-2.5}$ among 25 "best" models. Estimates combined using Bayesian model averaging.
Smith et al. (2000)	Phoenix, AZ (within city and within county), 1995-1997.	$PM_{2.5}$, $PM_{10-2.5}$	Significant linear relationship with $PM_{10-2.5}$, not $PM_{2.5}$. Piecewise linear models with possible $PM_{10-2.5}$ threshold for elderly mortality 20-25 $\mu g/m^3$
Gamble (1998)	Dallas, TX 1990-1994	PM_{10}, O_3, CO, NO_2, SO_2	O_3, CO, NO_2 significantly associated with mortality, PM_{10} and NO_2 not associated
Ostro (1995)	San Bernardino and Riverside Counties, CA 1980-1986.	$PM_{2.5}$ estimated from visual range, O_3	Positive, significant $PM_{2.5}$ effect only in summer
Kelsall et al. (1997)	Philadelphia, PA 1974-1988	TSP, SO_2, NO_2, O_3, CO	TSP, O_3, CO, NO_2 significant alone, TSP effect reduced when SO_2 included.
Moolgavkar and Luebeck (1996)	Philadelphia, PA 1973-1988	TSP, O_3, NO_2, SO_2.	NO_2 most significant pollutant, TSP effects stronger in summer and fall.
Murray and Nelson (2000)	Philadelphia, PA, 1973-1990	TSP only	Kalman filtering used to estimate hazard function in a state space model. Both TSP and the product of TSP and average temperature are significant, but not together. Includes estimate of at-risk population.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY**

Reference	Location(s)	Pollutants in Models	Comments
Single-City Mortality Studies in the U.S. and Canada			
Neas et al. (1999)	Philadelphia, PA 1973-1980	TSP only	Case-crossover study. Significant TSP effect.
Schwartz (2000d)	Philadelphia, PA 1974-1988	TSP, SO2, humidity-corrected extinction coefficient	No SO_2 effect when TSP in model. TSP significant unless extinction coefficient in model.
Burnett et al. (1998b)	Toronto, ON, Canada 1980-1994	TSP, CoH, $SO_4^=$, CO, NO_2, SO_2, O3, PM_{10} and $PM_{2.5}$ estimated from every-sixth-day data and observed daily $SO_4^=$, TSP, and CoH	Significant excess total mortality for $PM_{2.5}$, PM_{10}, TSP
Goldberg et al. (2001a,b,c,d)	Montreal, PQ, Canada, 1984-1995	$PM_{2.5}$ and PM_{10} every sixth day until 1992, daily through 1993. CO, NO_2, NO, O_3, SO_2. Missing PM data estimated from sulfates, CoH, extinction coefficient.	Excess total and cause-specific mortality with most PM indices reported (estimated $PM_{2.5}$, sulfates, CoH). In the age 65+ age group, total mortality significantly elevated in individuals with prior cancer, acute lower resp. disease, any cardiovascular disease, chronic coronary artery disease, congestive heart failure.
Ozkaynak et al. (1996)	Toronto, ON, Canada 1970-1991	TSP, CoH, O_3, CO, NO_2, SO_2	Significant association with 0-day lag TSP. Factor analysis identified a factor with high loadings on CoH, CO, and NO_2 (traffic presumably) significantly associated with total and most cause-specific deaths.

1   observations (e.g., days) and total number of events (i.e., total deaths), and the inverse variance

2   for the principal effect estimate are all important indices useful in determining the likely

3   precision of health effects estimates and in according relative scientific weight to the findings of

4   a given study.

5   As can be seen in Tables 8-1 and 8A-1, with a few exceptions, nearly all of the newly

6   reported analyses continue to show statistically significant associations between short-term (24 h)

7   PM exposures indexed by a variety of ambient PM measurements and increases in daily mortality

8   in numerous U.S. and Canadian cities, as well as elsewhere around the world. Also, the effects

9   estimates from the newly reported studies are generally consistent with those derived from the

10   earlier 1996 PM AQCD assessment, with the newly reported PM risk estimates generally falling

11   within the range of ca. 1 to 8% increase in excess deaths per 50 μg/m^3 PM$_{10}$ and ca. 2 to 6%

12   increase per 25 μg/m^3 PM$_{2.5}$. Several newly available PM epidemiology studies which

13   conducted time-series analyses in multiple cities are of particular interest, as discussed below.

14

15   **8.2.2.3 New Multi-City Studies**

16   The new multi-city studies are of particular interest here due to their evaluation of a wide

17   range of PM exposures and large numbers of observations holding promise of providing more

18   precise effects estimates than most smaller scale independent studies of single cities. Another

19   major advantage of the multi-city studies, over meta-analyses for multiple "independent" studies,

20   is the consistency in data handling and model specifications, which eliminates variation due to

21   study design. Further, unlike regular meta-analysis, they clearly do not suffer from potential

22   omission of negative studies due to "publication bias". Furthermore, geographic patterns of air

23   pollution effects can be systematically evaluated in multiple-city analyses. Thus, the results from

24   multi-city studies can provide especially valuable evidence regarding the consistency and/or

25   heterogeneity, if any, of PM-health effects relationships across geographic locations. Also, many

26   of the cities included in these multi-city studies were ones for which no time-series analyses had

27   been previously reported.

28

29

30

1   *8.2.2.3.1 U.S. Multi-City Studies*

2   **U.S. PM_{10} 20-Cities and 90-Cities NMMAPS Analyses**

3   The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-

4   series analyses of PM_{10} effects on mortality during 1987-1994 in the 90 largest U.S. cities (Samet

5   et al., 2000a,b), in the 20 largest U.S. cities in more detail (Dominici et al., 2000a), and PM_{10}

6   effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b). These

7   NMMAPS analyses are marked by extremely sophisticated statistical approaches addressing

8   issues of measurement error biases, co-pollutant evaluations, regional spatial correlation, and

9   synthesis of results from multiple cities by hierarchical Bayesian meta-regressions and

10   meta-analyses. These analyses provide extensive new information of much importance in being

11   among that most highly relevant to the setting of U.S. PM standards, because no other study has

12   examined as many U.S. cities in such a consistent manner. NMMAPS used only one consistent

13   PM index (PM_{10}) across all cities (noted PM_{10} samples were only collected every 6 days in most

14   of the 90 cities); death records were collected in a uniform manner; and demographic variables

15   were uniformly addressed. Both the 20 and 90 cities analyses studies employ multi-stage models

16   (see Table 8-1) in which heterogeneity in individual cities' coefficients in the first stage GAM

17   Poisson models were evaluated in the second stage models with city or region specific

18   explanatory variables.

19   In both the 20 and 90 cities studies, the combined estimates of PM_{10} coefficients were

20   positively associated with mortality at all the lags examined (0, 1, and 2 day lags), although the

21   1-day lag PM_{10} resulted in the largest overall combined estimate. Figure 8-3 shows the estimated

22   percent excess total deaths per 10 $\mu g/m^3$ PM_{10} at lag 1 day in the 88 (90 minus Honolulu and

23   Anchorage) largest cities, as well as (weighted average) combined estimates for U.S. geographic

24   regions depicted in Figure 8-4. The majority of the coefficients were positive for the various

25   cities listed along the left axis of Figure 8-3. The estimates for the individual cities were first

26   made independently, without borrowing information from other cities. The cities were then

27   grouped into the 7 regions seen in Figure 8-4 (based on characteristics of the ambient PM mix

28   typical of each region, as delineated in the 1996 PM AQCD). The bolded segments represent the

29   posterior means and 95% posterior intervals of the pooled regional effects under the more

30   conservative prior A for the heterogeneity across both regions and cities within regions. The

31   solid circles and squares denote, respectively, the overall regional means without and with
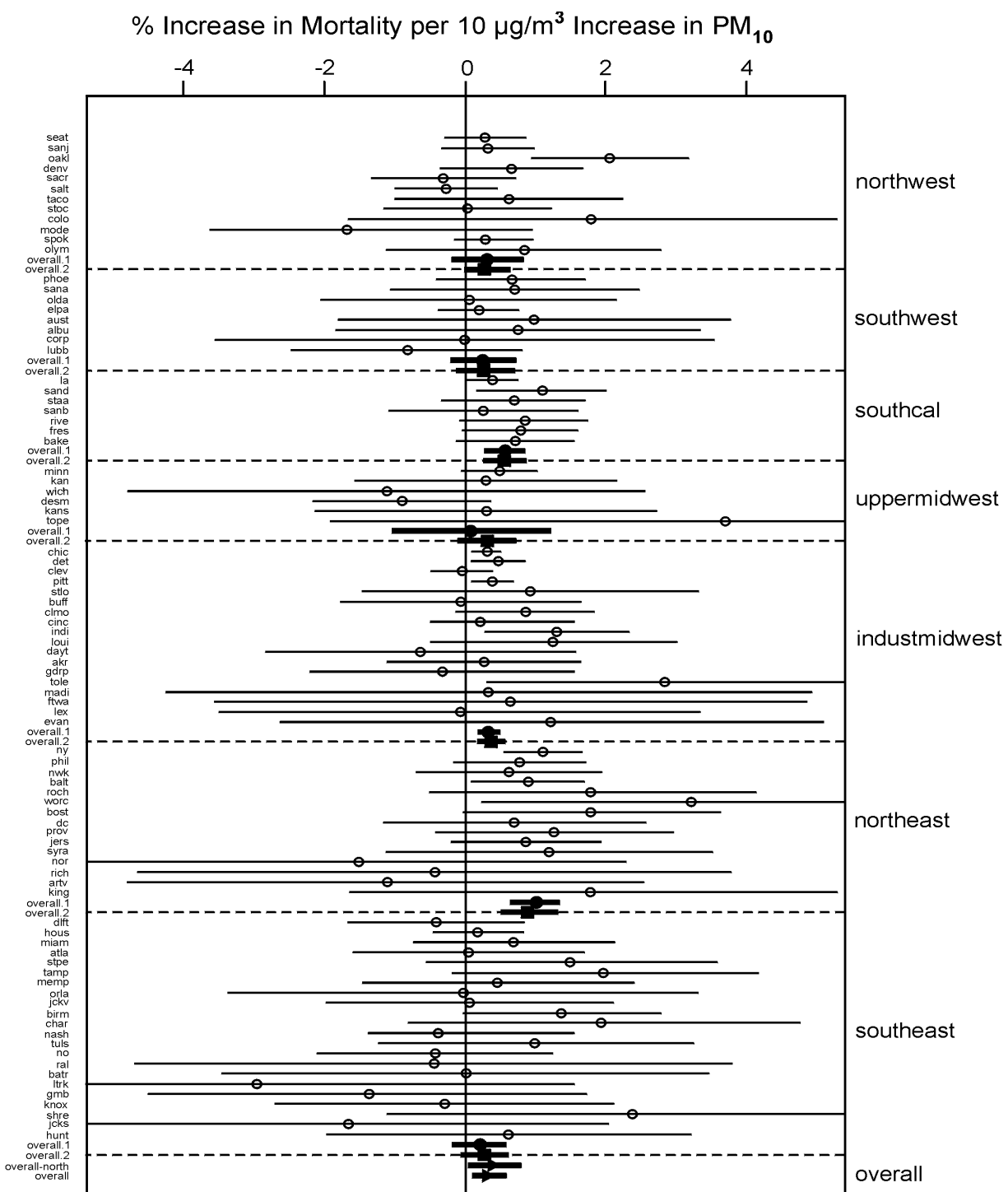
Figure 8-3. Estimated excess risks for PM mortality (1 day lag) for the 90 largest U.S. cities as shown in the original NMAPS report. From Samet et al. (2000a,b).
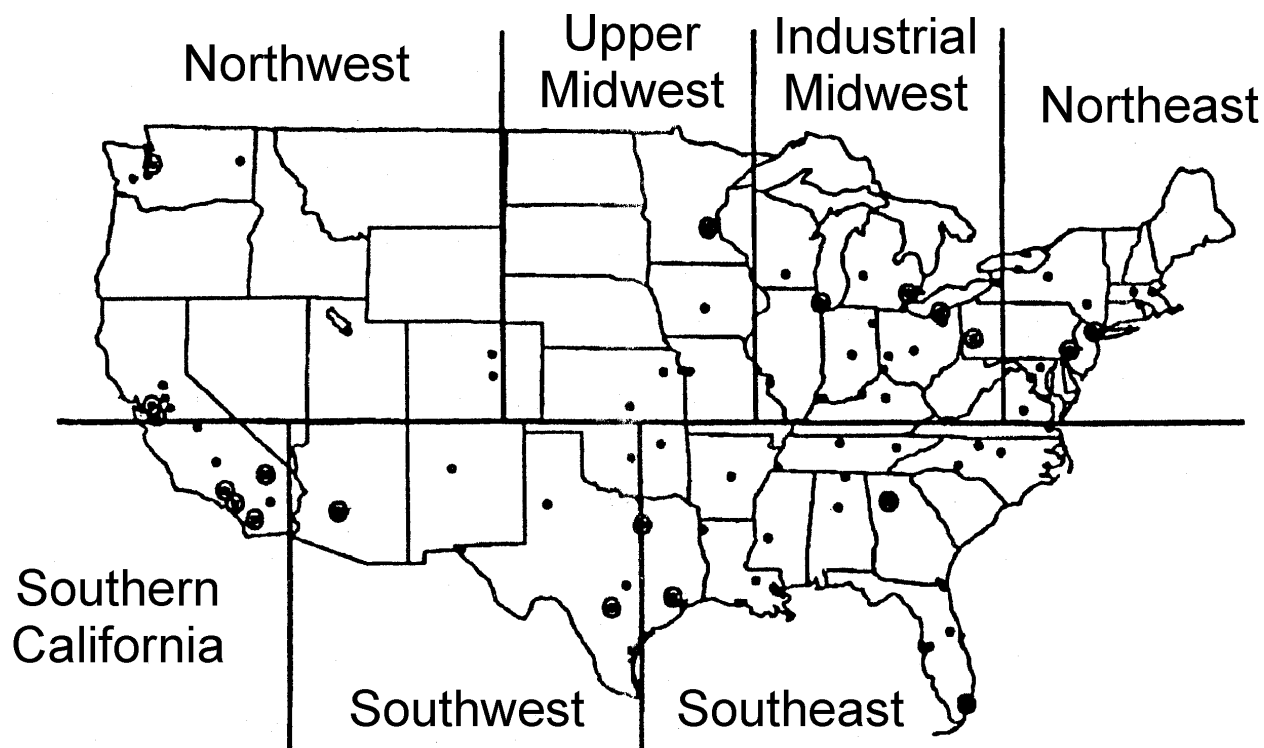
Figure 8-4. Map of the United States showing the 90 cities (the 20 cities are circled) and the seven regions considered in the NMMAPS geographic analyses. Regions: Northwestern; Southern California; Southwest; Upper Midwest; Industrial Midwest; Northeast; Southeast.

1   borrowing information from other regions, ("overall 1" = the regional mean without other

2   regions, "overall 2" = with information from other regions). The triangles and bolded segments

3   at the bottom of Figure 8-3 display combined estimates of nationwide overall effects of PM_{10} for

4   all cities overall, and for all cities minus those in the Northeast (overall-north).

5   Note that there appears to be some regional-specific variation in the overall combined

6   estimates, shown as "overall 1" and "overall 2" for the two sets of modeling assumptions and

7   specifications used in analyses combining data from all the cities in a given region. This can be

8   discerned more readily in Figure 8-5 (which depicts overall region-specific excess risk estimates

9   for day 0 and 2 day lags, as well as for lag 1 day). For example, the coefficients for the Northeast

10   are generally higher than for other regions (the Northeast combined estimate, 4.5% excess total

11   deaths per 50 μg/m^3 increase in PM_{10}, was about twice that for the 90-cities overall). The overall
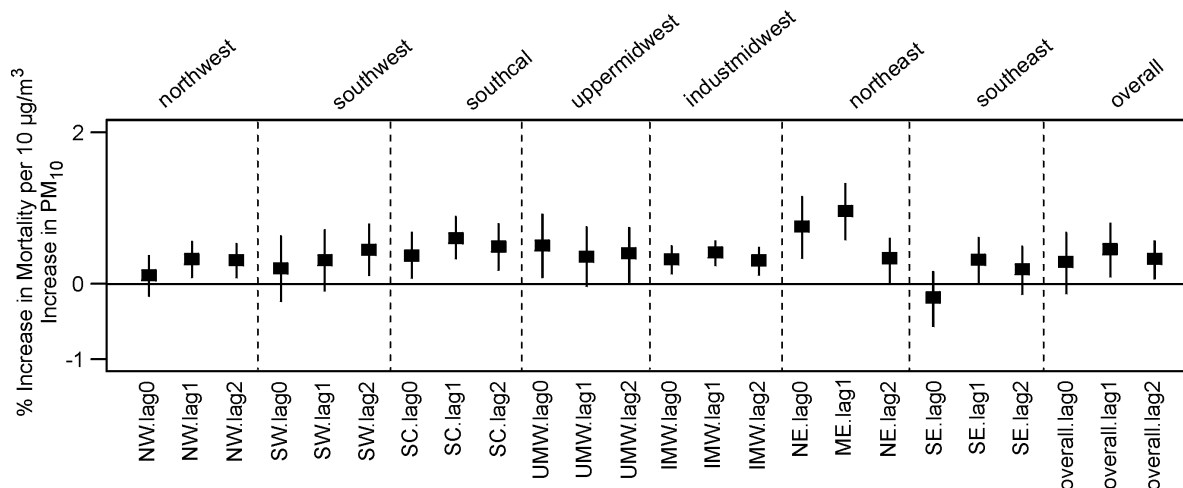
Figure 8-5. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-μg/m^3 increases in PM$_{10}$ concentrations in cities aggregated within U.S. regions shown in Figure 8-2.

1   national combined estimate (i.e., at lag 1 day, 2.3% excess total deaths per 50 μg/m^3 increase in

2   PM$_{10}$) for the 90 cities is consistent with the range of estimates reported in the 1996 PM AQCD.

3   In the 90 cities study, the weighted second-stage regression included five types of county-

4   specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude mortality

5   rate); (3) sociodemographic variables (% not graduating from high school and median household

6   income); (4) urbanization (public transportation); (5) variables related to measurement error

7   (median of all pair-wise correlations between monitors). Some of these variables were

8   apparently correlated (e.g., mean PM$_{10}$ and NO$_2$, household income and education) so that the

9   sign of coefficients in the regression changed when correlated variables were included in the

10   model. Thus, while some of the county-specific variables were statistically significant (e.g.,

11   mean NO$_2$ levels), interpreting the role of these county-specific variables may require caution.

12   Regarding the heterogeneity of PM$_{10}$ coefficients, the investigators concluded that they "did not

13   identify any factor or factors that might explain these differences".

14   Another important finding from Samet and coworkers' analyses was the weak influence of

15   gaseous co-pollutants on the PM$_{10}$ effect size estimates. In both the 20 and 90 cities analyses,

16   PM$_{10}$ coefficients changed little when O$_3$ was added to regression models. Additions of a third

17   pollutant (i.e., PM$_{10}$ + O$_3$ + another gaseous pollutant) did reduce PM$_{10}$ coefficients somewhat

1   (e.g., from ≈2.2 to ≈1.7 per 50 $\mu g/m^3$ PM_{10} at lag 1 day in the combined 90 cities analysis), but

2   the PM_{10} coefficients remained statistically significant at p< 0.05. The gaseous pollutants

3   themselves in single-, two-, and three-pollutant models were less consistently associated with

4   mortality than PM_{10}. Ozone was not associated with mortality using year-round data; but, in

5   season-specific analyses, it was associated with mortality negatively in winter and positively in

6   summer. SO_2, NO_2, and CO were weakly associated with mortality, but additions of PM_{10} and

7   other gaseous pollutants did not always reduce their coefficients, possibly suggesting their

8   independent effects. As noted in Section 8.1, CO and NO_2 from motor vehicles are likely

9   confounders of $PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the coarse particle fraction.

10 The investigators concluded that the PM_{10} effect on mortality "did not appear to be affected by

11 other pollutants in the model".

12

13 **U.S. 10-Cities Studies**

14   In another set of multi-city analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000),

15 Zanobetti and Schwartz (2000), Braga et al. (2000), and Braga et al. (2001) analyzed 1987-1995

16 air pollution and mortality data from ten U.S. cities (New Haven, CT; Pittsburgh, PA;

17 Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado

18 Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of

19 these cities was based on the availability of daily (or near daily) PM_{10} data. The main results of

20 the study were presented in the Schwartz (2000a) paper and the other studies noted above

21 focused on each of several specific issues, including: potential confounding, effect modification,

22 distributed lag, and threshold. In this section, the results for the Schwartz (2000a) main analyses

23 and that of Braga et al. (2000) on confounding are discussed, and results for analyses of other

24 specific issues are discussed later in appropriate sections. For each of the 10 cities, daily total

25 (non-accidental) mortality was fitted using a GAM Poisson model adjusting for temperature,

26 dewpoint, barometric pressure, day-of-week, season, and time. Deaths stratified by location of

27 death (in or outside hospital) were also examined. The data were also analyzed by season

28 (November through April as heating season). In the second stage, the PM_{10} coefficients were

29 modeled as a function of city-dependent covariates including co-pollutant to PM_{10} regression

30 coefficient (to test potential confounding), education, unemployment rate, poverty level, and

31 percent non-white. Threshold effects were also examined. The inverse variance weighted

1   averages of the ten cities' estimates were used to combine results. PM_{10} was significantly

2   associated with total deaths, and the effect size estimates were the same in summer and winter.

3   Adjusting for other pollutants did not substantially change the PM_{10} effect size estimates. The

4   socioeconomic variables did not modify the estimates. The effect size estimates for the deaths

5   outside hospital were substantially greater than for inside hospital. The combined percent excess

6   death estimate for total mortality was 3.4% (95% CI: 2.7-4.1) per 50 $\mu g/m^3$ increase in PM_{10}, but

7   was larger for days with $PM_{10} < 50 \mu g/m^3$.

8   Braga et al. (2000) evaluated potential confounding of the reported PM-mortality

9   associations by effects of respiratory epidemics, using data from a subset of 5 of the 10 cities

10   evaluated by Schwartz (2000a). When adjustments were made for respiratory epidemics, small

11   decreases in PM_{10} effects were seen in the cities evaluated. The overall estimated percent excess

12   deaths per 50 $\mu g/m^3$ PM_{10} for the five cities was 4.3% (CI 3.0, 5.6) without control for respiratory

13   epidemics, but slightly decreased to 4.0% (CI 2.6, 5.3) with control for epidemics.

14

15   **U.S. 3-Cities Study**

16   Moolgavkar (2000a) evaluated associations between short-term measures of major air

17   pollutants and daily deaths in three large U.S. metropolitan areas (Cook Co., IL, encompassing

18   Chicago; Los Angeles Co., CA; and Maricopa Co., AZ, encompassing Phoenix) during a 9-year

19   period (1987-1995). Generalized additive models (GAM) were used in a standard manner to

20   conduct time-series Poisson regression analyses independently for each of the three cities

21   (allowing comparison of results across them not due to methodological differences), but no

22   combined analyses were attempted to derive overall PM effects estimates. Total non-accidental

23   deaths and cause-specific deaths from cardiovascular disease (CVD), cerebrovascular disease

24   (CrD), and chronic obstructive lung disease (COPD), and associated conditions were analyzed in

25   relation to 24-h readings for PM, O_3, CO, NO_2, SO_2 averaged over all monitors in a given county.

26   Daily readings were available for each of the gaseous pollutants in all three countries, as were

27   PM_{10} values for Cook County. However, PM_{10} values were only available every sixth day in

28   Maricopa and Los Angeles Counties; as were $PM_{2.5}$ values in Los Angeles Co. PM values were

29   highest in the winter and fall in Los Angeles Co., in the fall in Maricopa Co., and in summer in

30   Cook Co., whereas the gases (except for O_3) were highest in winter in all three counties (O_3 was

31   highest in summer in all three). The PM indices were moderately correlated (r = 0.30 to 0.73)

1   with CO, NO$_2$, and SO$_2$ in Cook Co. and Los Angeles Co., but poorly correlated (r < 0.22) with

2   those gases in Maricopa Co. Ozone was very poorly (r < 0.20) or negatively correlated with PM

3   or the other gases in each location (except for Cook Co., r = 0.36 for O$_3$ vs PM$_{10}$). Total

4   non-accidental, CVD, and COPD deaths were all highest during winter in all three counties, but

5   CrD deaths were relatively constant from season to season (no season-specific analyses reported).

6   Controlling for temperature and relative humidity effects in separate analyses for each

7   mortality endpoint for each of the three countries, varying patterns of results were found from

8   one location to another, as noted in Table 8A-1. In general, although PM$_{10}$ in each of the three

9   counties (and PM$_{2.5}$ in Los Angeles) and each of the gaseous pollutants (except O$_3$) were all

10   statistically significantly associated with total non-accidental mortality at one or more lag times

11   (0 to 5 days) in single pollutant models, the PM effect estimates tended to be reduced and non-

12   significant in many of the multi-pollutant (PM plus one other gas or PM plus all others) analyses.

13   In contrast, effect estimates for several of the gases (CO, SO$_2$, and NO$_2$) tended to be more robust

14   than those for PM in multi-pollutant models, with their estimates remaining statistically

15   significant (although usually somewhat attenuated) at one or more lag times when included in

16   multi-pollutant models with PM$_{10}$ or PM$_{2.5}$. Similarly, a somewhat analogous varying pattern of

17   results was observed for the cause-specific mortality analyses (discussed further below in Section

18   8.2.2.5). That is, although PM$_{10}$ or PM$_{2.5}$ were statistically significantly related to CVD and

19   COPD-related (and to CrD only in Maricopa Co., lag 5) mortality in single pollutant models,

20   their coefficients were typically markedly reduced and became non-significant in multi-pollutant

21   analyses with one or more of the gases included in the model. Moolgavkar (2000a) concluded

22   that, while direct effects of individual components of air pollution cannot be ruled out, individual

23   components can best be thought of as indices of the overall air pollution mix; and he noted

24   considerable heterogeneity of air pollution effects across the three geographic areas evaluated.

25   Moolgavkar (2000a) did not calculate any pooled effect estimates possibly because of the

26   heterogeneity seen among the cities studied.

27

28   *8.2.2.3.2 Canadian Multi-City Study Analyses*

29   **Urban Air Pollution Mix and Daily Mortality in 11 Canadian Cities**

30   The number of daily deaths for non-accidental causes during 1980-1991 were obtained for

31   11 Canadian cities and linked to concentrations of ambient gaseous air pollutants using relative

1   risk regression models for longitudinal count data (Burnett et al., 1998a). The GAM Poisson

2   models used evaluated daily mortality versus O_3, NO_2, SO_2 and CO (including adjustments for

3   seasonal cycles, day-of-week effects, and weather effects), but no PM indices were included in

4   their analyses because daily PM measurements were not available. However, data were available

5   for fine and coarse PM mass from dichot samples, and sulfates, on variable schedules somewhat

6   more frequently than once per six days in Montreal, Toronto, and Windsor (with smaller

7   numbers in the other cities). This allowed an ecologic comparison of gaseous pollutant risks by

8   mean fine particle concentration (their Figure 1). These comparisons suggested a weak negative

9   confounding of NO_2 and SO_2 effects with fine particles, and a weak positive confounding of

10   particle effects with O_3.

11

12   **Eight Largest Canadian Cities Study**

13   Burnett et al. (2000) analyzed various PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, COH, and

14   47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants

15   (NO_2, O_3, SO_2, and CO) for association with total mortality in the 8 largest Canadian cities:

16   Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This

17   study differs from (Burnett et al., 1998a), including fewer cities but more recent years of data

18   (1986-1996 vs. 1980-1991) and detailed analyses of particle mass components by size and

19   elemental composition. Each city's mortality, pollution, and weather variables were separately

20   filtered for seasonal trends and day-of-week patterns. The residual series from all cities were

21   then combined and analyzed in a GAM Poisson model. The weather model was selected from

22   spline-smoothed functions of temperature, relative humidity, and maximum change in barometric

23   pressure within a day and with 0 and 1 day lags, using forward stepwise procedures. Pollution

24   effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-

25   pollutant models, principal components were also used as predictors in the regression models.

26   Ozone was weakly correlated with other pollutants, and other pollutants were "moderately"

27   correlated with each other (the highest was r = 0.65 for NO_2 and CO). The strongest association

28   with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger

29   predictor of mortality than $PM_{10-2.5}$. The gaseous pollutant effects estimates were generally

30   reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10-2.5}$, where strength of prediction is measured

31   by the t value or statistical significance of the excess risk. In addition to the results implicating

1   the fine particle fraction ($PM_{2.5}$) most clearly, other findings on fine particle components were

2   also of interest. Specifically, sulfate, Fe, Ni, and Zn were most strongly associated with

3   mortality. The total effect of these four components was greater than that for $PM_{2.5}$ mass alone,

4   the authors suggesting that the characteristics of the complex chemical mixture in the fine

5   fraction may be a better predictor of mortality than the mass index alone.

6

7   *8.2.2.3.3 European Multi-City APHEA Study Analyses*

8   The Air Pollution and Health: a European Approach (APHEA) project is a multi-center

9   study of short-term effects of air pollution on mortality and hospital admissions with a wide

10   range of geographic, climatic, sociodemographic, and air quality patterns. The obvious strength

11   of this approach is to be able to evaluate potential effect modifiers in a consistent manner.

12   It should be noted that PM indices measured in those cities varied. In APHEA1, the PM indices

13   measured were mostly black smoke (BS), except for: Paris, Lyon (PM_{13}); Bratislava, Cologne,

14   and Milan (TSP); and Barcelnoa (BS and TSP). In APHEA2, 10 out of the 29 cities used actual

15   PM_{10} measurements; in 11 additional cities, PM_{10} levels were estimated based on regression

16   models relating collocated PM_{10} measurements to BS or TSP. In the remaining 8 cities, only BS

17   measurements were available (14 cities had BS measurements). As discussed below, there have

18   been several papers published that present either a meta-analysis or pooled summary estimates of

19   these multi-city mortality results: (1) Katsouyanni et al. (1997) — SO_2 and PM results from

20   12 cities; (2) Touloumi et al. (1997) — ambient oxidants (O_3 and NO_2) results from six cities;

21   (3) Zmirou et al. (1998) — cause-specific mortality results from 10 cities (see Section 8.2.2.5);

22   (4) Samoli et al. (2001) — a reanalysis of APHEA1 using a different model specification to

23   control for long-term trends and seasonality; and (5) Katsouyanni et al. (2001) — APHEA2, with

24   emphasis on the examination of confounding and effect modification.

25

26   **APHEA1 Sulfur Dioxide and Particulate Matter Results for 12 Cities**

27   The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens,

28   Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyons, Milan, Paris, Poznan, and

29   Wroclaw. In the western European cities, an increase of 50 $\mu g/m^3$ in SO_2 or BS was associated

30   with a 3% (95% CI = 2.0, 4.0) increase in daily mortality; and the corresponding figure was 2%

31   (95% CI = 1.0, 3.0) for estimated PM_{10} (they used conversion: $PM_{10} = TSP*0.55$). In the

1   central/eastern European cities, the increase in mortality associated with a 50 μg/m^3 change was

2   0.8% (CI = $^-$0.1, 2.4) for SO$_2$ and 0.6% (CI = 0.1, 1.1) per 50 μg/m^3 change in BS. Estimates of

3   cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to

4   those for one day effects. The effects of both pollutants (BS, SO$_2$) were stronger during the

5   summer and were mutually independent. Regarding the contrast between the western and

6   central/eastern Europe results, the authors speculated that this could be due to: difference in

7   exposure representativeness; difference in pollution toxicity or mix; difference in proportion of

8   sensitive sub-population; and model fit for seasonal control. Bobak and Roberts (1997)

9   commented that the heterogeneity between central/eastern and western Europe could be due to

10   the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted that,

11   having examined the source of heterogeneity, other factors could apparently explain the

12   difference in estimates as well as or better than temperature.

13

14   **APHEA1 Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities**

15   Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated

16   (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents),

17   and (b) impacts on effect estimates for NO$_2$ and O$_3$ of including a PM measure (BS) in

18   multi-pollutant models. Six cities in central and western Europe provided data on daily deaths

19   and NO$_2$ and/or O$_3$ levels. Poisson autoregressive models allowing for overdispersion were

20   fitted. Significant positive associations were found between daily deaths and both NO$_2$ and O$_3$.

21   Increases of 50 μg/m^3 in NO$_2$ (1-hour maximum) or O$_3$ (1-hour maximum) were associated with

22   a 1.3% (95% CI 0.9-1.8) and 2.9% (95% CI 1.0-4.9) increase in the daily mortality, respectively.

23   There was a tendency for larger effects of NO$_2$ in cities with higher levels of BS: when BS was

24   included in the model, the pooled estimate for the O$_3$ effect was only slightly reduced, but the

25   coefficient for NO$_2$ was reduced by half (but remained significant). The authors speculated that

26   the short-term effects of NO$_2$ on mortality might be confounded by other vehicle-derived

27   pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study

28   reports only relative risk levels for NO$_2$ and O$_3$ (but not for BS), it illustrates the importance of

29   confounding of NO$_2$ and PM effects and the relative limited confounding of O$_3$ and PM effects.

30

31

APHEA1: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality

In order to investigate further the source of the regional heterogeneity of PM effects and to examine the sensitivity of the RRs, the APHEA1 data were reanalyzed by APHEA investigators (Samoli et al., 2001). Unlike previous analysis (i.e., analysis by Katsouyanni et al., 1997) in which sinusoidal terms for seasonal control and polynomial terms for weather were used, the investigators this time used a GAM model with smoothing terms for seasonal trend and weather, which is a more commonly used approach in recent years. Using this model, the estimated relative risks for central-eastern cities were larger than those obtained in the previous analysis, reducing the contrast of estimated PM effects between central-eastern and western European cities. Also, restricting the analysis to days with concentration < 150 ug/m^3 further reduced the differences between the western and central-eastern European cities. The authors conclude that part of the heterogeneity in the estimated air pollution effects between western and central-eastern cities in previous publications was caused by the statistical approach and the data range. These results indicate that the apparent regional heterogeneity could be somewhat sensitive to model specification. Since the number of cities used in the APHEA1 study is relatively small (eight western and five central-eastern cities), the apparent regional heterogeneity found in the earlier publications could also be due to chance. Thus, such heterogeneity may be sensitive to model specification and/or choice of data range. The combined estimate for 50 μg/m^3 increase in PM$_{10}$ was reported to be 3.3% (95CI: 2.6, 4.1)

APHEA2: Confounding and Effect Modification Using Extended Data

The APHEA2 analyses (Katsouyanni et al. 2001) included more cities (29 cities) and a more recent study period (variable years in 1990-1997, as compared to 1975-1992 in APHEA1). As with the recent reanalysis of APHEA1 by Samoli et al. (2001), APHEA2 analyses used a GAM Poisson model with a smoother to control for season and trends. The analyses put emphasis on effect modification by city-specific factors. Thus, the city-specific coefficients from the first stage of Poisson regressions were modeled in the second stage regression using city-specific characteristics as explanatory variables. Inverse-variance weighted pooled estimates (fixed-effects model) were obtained as part of this model. When substantial heterogeneity was observed, the pooled estimates were obtained using random-effects models. These city-specific variables included: (1) air pollution level and mix, such as average air pollution levels and

1   PM/NO$_2$ ratio (as an indicator of traffic-generated PM); (2) climatic variables, such as mean

2   temperature and relative humidity; (3) health status of the population, such as the age-adjusted

3   mortality rates, the percentage of persons over 65 years of age, and smoking prevalence;

4   (4) geographic area (three regions: central-eastern, southern, and north-western). The study also

5   addressed the issue of confounding by simultaneous inclusion of gaseous co-pollutants in city-

6   specific regressions, and obtaining the pooled PM estimates for each co-pollutant included.

7   Unlike APHEA1, in which the region (larger PM estimates in western Europe than in

8   central-eastern Europe) was highlighted as the important factor, APHEA2 found several effect

9   modifiers. NO$_2$ (i.e., index of high pollution from traffic) was an important one. The cities with

10 higher NO$_2$ levels showed larger PM effects. That is, the estimated PM$_{10}$ risk was approximately

11 4-fold in cities with NO$_2$ levels in the 75th percentile ("high"), as compared to cities with NO$_2$

12 levels in the 25th percentile ("low") of the distribution. The cities with warmer climate showed

13 larger PM effects. The investigators noted that this might be due to the better estimation of

14 population exposures with outdoor community monitors (because of more open windows). Also,

15 the cities with low standardized mortality rate showed larger PM effects. The investigators

16 speculated that this may be because a smaller proportion of susceptible people (to air pollution)

17 are available in a population with a large age-standardized mortality rate. Interestingly, in the

18 pooled PM risk estimates from models with gaseous pollutants, it was also NO$_2$ that affected

19 (reduced) PM risk estimates most. For example, in the fixed-effects models, approximately 50%

20 reductions in both PM$_{10}$ and BS coefficients were observed when NO$_2$ was included in the model.

21 SO$_2$ only minimally reduced PM coefficients, whereas O$_3$ actually increased PM coefficients.

22 Thus, in this analysis, NO$_2$ was implicated both as a confounder and an effect modifier. The

23 overall combined estimate for total mortality for PM$_{10}$ or BS was 3.0% (95CI: 2.0, 4.1).

24

25 *8.2.2.3.4 An Examination of Effect Modification Using Past Results*

26   Levy et al. (2000) sought to explain the apparent heterogeneity of PM effects found in past

27 studies. Their analysis is different from the other multi-city studies discussed above in that they

28 analyzed the PM coefficients from past studies, rather than obtaining city-specific coefficients in

29 a consistent time-series model specification. However, their results are worth mentioning here,

30 as they examined various city-specific covariates that are similar to those examined in other

31 multi-city studies, as well those that are unique to their study. They applied an empirical Bayes

1   meta-analysis to 29 PM estimates from 21 published studies; and, in a second stage regression,

2   they considered city-specific variables such as mortality rate, gaseous pollutants' regression,

3   coefficients (that is, regressing a gaseous pollutant on PM), PM_{10} levels, $PM_{2.5}/PM_{10}$ ratio, central

4   air conditioning prevalence, and heating/cooling degree days. Among these variables,

5    $PM_{2.5}/PM_{10}$ ratio was a significant predictor (larger PM estimates for higher $PM_{2.5}/PM_{10}$ ratio)

6   in the 19 U.S. cities data subsets. While sulfate data were not available for all the 19 studies, the

7   investigators noted that the sulfate/PM_{10} ratio was highly correlated with both the mortality

8    $(r = 0.84)$ and with the $PM_{2.5}/PM_{10}$ ratio in the limited subset of data, indicating that the

9   sulfate/PM_{10} ratio could be an even better predictor of regional heterogeneity of PM risk

10   estimates. It would be interesting to estimate $PM_{2.5}/PM_{10}$ ratios or sulfate/PM_{10} ratios for a larger

11   U.S. dataset (e.g., Samet et al.'s 90 cities study) and examine if Levy et al.'s finding holds for

12   larger geographic coverage. After adjusting for city-specific covariates, Levy et al.'s combined

13   total mortality excess death estimate for the 19 U.S. PM studies was 3.5% (95% CI: 2.7, 4.4) per

14   50 $\mu g/m^3$ increase in PM_{10}.

15

16   *8.2.2.3.5 Comparison of Effects Estimates from Multi-City Studies*

17   In summary, based on pooled analyses of data combined across multiple cities, the percent

18   excess (total, non-accidental) deaths estimated per 50 $\mu g/m^3$ increase in PM_{10} in the above

19   multi-city studies were: (1) 2.3% in the 90 largest U.S. cities (4.5% in the Northeast region);

20   (2) 3.4% in 10 U.S. cities; (3) 3.5% in the 8 largest Canadian cities; and (4) 2.0% in western

21   European cities (using $PM_{10} = TSP*0.55$) in the original APHEA1; (5) 3.3% in the reanalysis of

22   APHEA1; (6) 3.0% in APHEA2; and (7) 3.5% in Levy et al.'s analysis of the 19 U.S. studies.

23   These combined estimates are all consistent with the range of PM_{10} estimates previously reported

24   in the 1996 PM AQCD.

25

26   **8.2.2.4 The Role of Particulate Matter Components**

27   Delineation of the roles of specific ambient PM components in contributing to associations

28   between short-term PM exposures and mortality requires evaluation of several factors, e.g., size,

29   chemical composition, surface characteristics, and presence of gaseous co-pollutants. While

30   possible combinations of interactions among these factors can in theory be limitless, the actual

31   data tend to cover definable ranges of aerosol characteristics and co-pollutant environments due

1   to typical source characteristics (e.g., fine particles tend to be combustion products in most

2   cities). Newly available studies conducted in the last few years have begun to provide more

3   extensive information on the issue of PM component roles; their results are discussed below in

4   relation to three topics: (1) PM particle size (e.g., $PM_{2.5}$ vs. $PM_{10-2.5}$); (2) chemical components;

5   and (3) source oriented evaluations.

6

7   *8.2.2.4.1 Particulate Matter Particle Size Evaluations*

8   Numerous studies published since the 1996 PM AQCD substantiate associations between

9     $PM_{2.5}$ and increased total mortality. Consistent with the 1996 PM AQCD findings, effect size

10   estimates from the new studies generally fall within the range of 2 to 6% excess total mortality

11   per 25 $\mu g/m^3$ $PM_{2.5}$, with many being statistically significant at p<0.05.

12   With regard to the relative importance of the fine and coarse fractions of inhalable PM_{10}

13   particles capable of reaching thoracic regions of the respiratory tract, at the time of the 1996 PM

14   AQCD, there was only one acute mortality study (Schwartz et al., 1996a) that examined this

15   issue. That study suggested that fine particles ($PM_{2.5}$), distinctly more so than coarse fraction

16   ($PM_{10-2.5}$) particles, were associated with daily mortality. A recent study (Klemm et al., 2000), to

17   reconstruct the data and to replicate the original analyses, essentially reproduced the original

18   investigators' results.

19   Since the 1996 PM AQCD, several new studies have used size-fractionated PM data to

20   investigate the relative importance of fine ($PM_{2.5}$) vs. coarse ($PM_{10-2.5}$) fraction particles.

21   Table 8-2 provides synopses of those studies with regard to the relative importance of the two

22   size fractions, as well as some characteristics of the data. The average levels of $PM_{2.5}$ ranged

23   from about 13 to 20 $\mu g/m^3$ in the U.S. cities, but much higher average levels were measured in

24   Mexico City (27.4 $\mu g/m^3$) and Santiago, Chile (64.0 $\mu g/m^3$). As can be seen in Table 8-2, in the

25   northeastern U.S. cities (Pittsburgh, Philadelphia, and Detroit) and Atlanta, GA, there was more

26     $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average, whereas in the western U.S. (Phoenix, AZ;

27   Coachella Valley, CA; Santa Clara County, CA) the average $PM_{10-2.5}$ levels were higher than

28     $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 8-2 use much the same

29   data set, using fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal

30   differences in PM component levels should also be noted. For example, in Santa Clara County

31   and in Santiago, Chile, the winter $PM_{2.5}$ levels averaged twice those during summer. The

TABLE 8-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10-2.5}$

Author, City	Means (μg/m^3); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10-2.5}$.	Results regarding relative importance of $PM_{2.5}$ vs. $PM_{10-2.5}$ and comments.
Fairley (1999). Santa Clara County, CA	$PM_{2.5}$ mean = 13; $PM_{2.5}/PM_{10}$ = 0.38; r = 0.51.	Of the various pollutants including PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, COH, CO, NO_2, and O_3, strongest associations were found for ammonium nitrate and $PM_{2.5}$. $PM_{2.5}$ was significantly associated with mortality, but $PM_{10-2.5}$ was not, separately and together in the model. Sulfate was a significant predictor of mortality in single pollutant model, but not when $PM_{2.5}$ was included simultaneously. Winter $PM_{2.5}$ level is more than twice that in summer.
Ostro et al. (2000). Coachella Valley, CA	$PM_{2.5}$ (Palm Springs and Indio, respectively) mean = 12.7, 16.8; $PM_{2.5}/PM_{10}$ = 0.43, 0.35; r = 0.46, 0.28.	Total mortality was more significantly associated with $PM_{2.5}$ than with $PM_{10-2.5}$. Cardiovascular mortality was associated with $PM_{10-2.5}$ more significantly than with $PM_{2.5}$, but their effect size estimates per IQR were similar.
Clyde et al. (2000). Phoenix, AZ	$PM_{2.5}$ mean = 13.8; $PM_{2.5}/PM_{10}$ = 0.30; r = 0.65.	Using Bayesian Model Averaging that incorporates model selection uncertainty, with 29 covariates (lags 0- to 3-day), effects of coarse particles (most consistent at lag 1 day) were found to be stronger than that for fine particles. The association was for mortality confined to the region where fine particles ($PM_{2.5}$) are expected to be uniform.
Mar et al. (2000). Phoenix, AZ 1995-1997.	$PM_{2.5}$ (TEOM) mean = 13; $PM_{2.5}/PM_{10}$ = 0.28; r = 0.42.	Total mortality was weakly (p < 0.10) associated with $PM_{10-2.5}$. It was less strongly (p > 0.10) associated with $PM_{2.5}$. Cardiovascular mortality was both significantly associated with $PM_{2.5}$ (lags 1, 3, 4) and $PM_{10-2.5}$ (lag 0).
Smith et al. (2000). Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, a statistically significant mortality association found with $PM_{10-2.5}$, but not with $PM_{2.5}$. In models allowing for a threshold, evidence of a threshold for $PM_{2.5}$ (in the range of 20-25 μg/m^3) suggested, but not for $PM_{10-2.5}$. Seasonal interaction in the $PM_{10-2.5}$ effect also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10-2.5}$ is lowest.
Lippmann et al. (2000). Detroit, MI 1992-1994.	$PM_{2.5}$ mean=18; $PM_{2.5}/PM_{10}$ =0.58; r = 0.42.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were positively associated with mortality outcomes to a similar extent. Simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$ also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a). Philadelphia, PA 1992-1995.	$PM_{2.5}$ mean=17.3; $PM_{2.5}/PM_{10}$ =0.72.	The authors conclude that no systematic differences were seen according to particle size or chemistry. However, when $PM_{2.5}$ and $PM_{10-2.5}$ were compared, $PM_{2.5}$ (at lag 1 or average of lag 0 and 1) was more significantly (with larger attributable risk estimates) associated with cardiovascular mortality than $PM_{10-2.5}$.

TABLE 8-2 (cont'd). SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10-2.5}$.	Results regarding relative importance of $PM_{2.5}$ vs. $PM_{10-2.5}$ and comments.
Klemm and Mason (2000). Atlanta, GA	$PM_{2.5}$ mean = 19.9; $PM_{2.5}/PM_{10}$ =0.65.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.
Klemm et al. (2000)	Mean $PM_{2.5}$ ranges from 11.3 in Portage to 29.6 in Steubenville. Mean $PM_{10-2.5}$ ranges from 6.6 in Portage to 16.1 in Steubenville. Mean $PM_{2.5}/PM_{10}$ ranges from 50.1% in Topeka to 66% in Kinston-Harriman.	Significant associations between total mortality and $PM_{2.5}$ in 3 cities and in pooled effect. No significant association with $PM_{10-2.5}$ in the replications study for any city.
Chock et al. (2000). Pittsburgh, PA	Data distribution not reported. $PM_{2.5}/PM_{10} \approx 0.67$.	Seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and small size of dataset stratified by age group and season limit confidence in results finding no consistently significant associations for any size fraction.
Burnett et al. (2000) 8 Canadian cities 1986-1996	$PM_{2.5}$ mean=13.3; $PM_{2.5}/PM_{10}$ =0.51; r = 0.37.	$PM_{2.5}$ was a stronger predictor of mortality than $PM_{10-2.5}$. For chemical species, sulfate ion, nickel, and zinc from the fine fraction were most strongly associated with mortality.
Castillejos et al. (2000). Mexico City. 1992-1995	$PM_{2.5}$ mean=27.4; $PM_{2.5}/PM_{10}$ =0.61; r = 0.52.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were associated individually with mortality, but the $PM_{10-2.5}$ effect size was larger and more significant. When both were included in the model, the effect size of $PM_{10-2.5}$ remained the same but that of $PM_{2.5}$ was virtually eliminated.
Cifuentes et al. (2000). Santiago, Chile 1988-1996.	$PM_{2.5}$ mean=64.0; $PM_{2.5}/PM_{10}$ =0.58; r = 0.52.	Results were different for warmer and colder months. $PM_{2.5}$ was more important than $PM_{10-2.5}$ in the whole year and in winter, but not in summer. The mean of $PM_{2.5}$ was more than twice higher in winter (82.4 $\mu g/m^3$) than in summer (32.8), whereas the mean of $PM_{10-2.5}$ was more comparable for winter (49.9 $\mu g/m^3$) and for summer (42.9).
Anderson et al. (2001). The west Midlands conurbation, UK. 1994-1996.	$PM_{2.5}$ mean=14.5; $PM_{2.5}/PM_{10}$ =0.62; r = 0.92.	No significant association seen between total mortality and any of the PM indices in the all year analysis, but PM_{10} and $PM_{2.5}$ were significantly associated with total mortality in the warm season (April-September). $PM_{10-2.5}$ was generally more weakly associated with mortality outcomes than PM_{10} or $PM_{2.5}$.

1   temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$ ranged between 0.30 and 0.65. Such differences

2   in ambient PM mix characteristics from season to season or from location to location

3   complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

4   To facilitate a quantitative overview of the effect size estimates and their corresponding

5   uncertainties from these studies, the percent excess risks are plotted in Figure 8-6. These

6   excluded the Clyde et al. study, in which the model specification did not obtain RRs for $PM_{2.5}$

7   and $PM_{10-2.5}$ separately, and the Smith et al. study, which did not present linear term RRs for

8    $PM_{2.5}$ and $PM_{10-2.5}$. Note that, in most of the original studies, the RRs were computed for

9   comparable distributional features (e.g., inter quartile range, mean, 5th-to-95th percentile, etc.).

10   However, the increments derived and their absolute values varied across studies; and therefore,

11   the RRs used in deriving the excess risk estimates delineated in Figure 8-6 were re-computed for

12   consistent increments of 25 $\mu g/m^3$ for both $PM_{2.5}$ and $PM_{10-2.5}$. Note also that re-computing the

13   RRs per 25 $\mu g/m^3$ in some cases changed the relative effect size between $PM_{2.5}$ and $PM_{10-2.5}$, but

14   it did not affect the relative significance.

15   All of the studies found positive associations between both the fine and coarse PM indices

16   and increased mortality risk, with most for $PM_{2.5}$ and a few for $PM_{10-2.5}$ being statistically

17   significant. However, most of the studies did not have large enough sample sizes to separate out

18   what often appear to be relatively small differences in effect size estimates; but several do show

19   statistical distinctly larger and significant mortality associations with $PM_{2.5}$ than for non-

20   significant $PM_{10-2.5}$ effects. For example, the Klemm et al. (2000) recomputation of the Harvard

21   Six Cities time-series study reconfirmed the original Schwartz et al. (1996a) finding of $PM_{2.5}$

22   being significantly associated with excess mortality, whereas $PM_{10-2.5}$ was not. Similar results

23   were obtained by the other multi-city study, i.e., the 8 largest Canadian cities study by Burnett

24   et al. (2000), and by the Atlanta (Klemm and Mason, 2000), Santa Clara (Fairley, 1999), and the

25   Coachella Valley (Ostro et al., 2000) studies. There were two studies in which the importance of

26   $PM_{2.5}$ and $PM_{10-2.5}$ were considered to be similar or, at least, not distinguishable: Philadelphia, PA

27   (Lipfert et al., 2000a) and Detroit, MI (Lippmann et al., 2000). The three Phoenix studies

28   obtained "mixed" results, in that the Smith et al. (2000) and Clyde et al. (2000) analyses (not

29   shown in Figure 8-6) found $PM_{10-2.5}$ to appear to be more important in explaining mortality than

30   $PM_{2.5}$, but Mar et al. (2000) found both to be significant (as depicted in Figure 8-6). Also, the

31   Mexico City analysis by Castillejos et al. (2000) implicated $PM_{10-2.5}$ as the apparent more
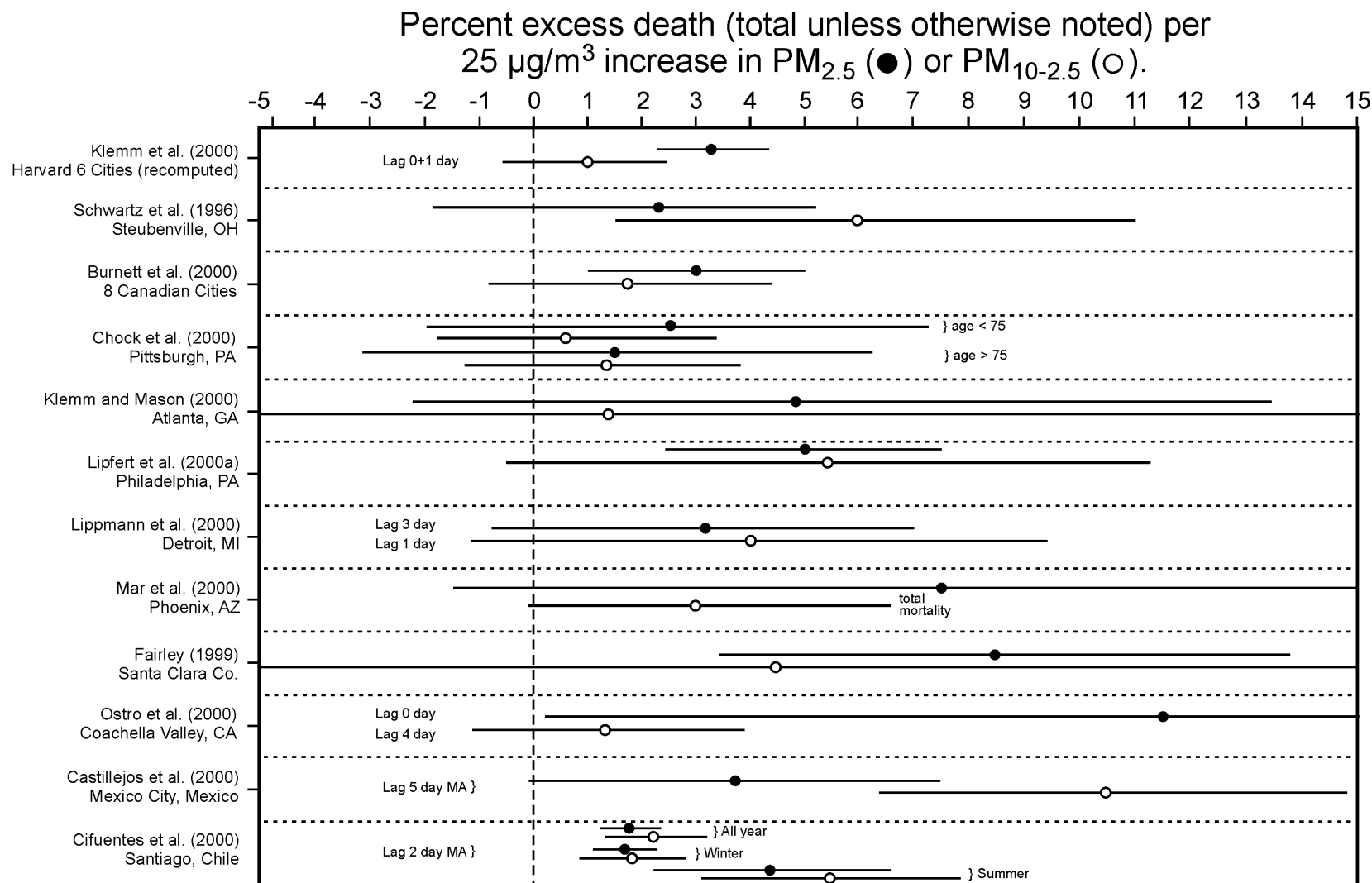
Figure 8-6. **Percent excess risks estimated per 25 μg/m³ increase in PM₂.₅ or PM₁₀₋₂.₅ from new studies evaluating both PM₂.₅ and PM₁₀₋₂.₅ data for multiple years, based on single pollutant (PM only) models. All lags = 1 day, unless indicated otherwise (See Section 8.4.2 for same studies shown here that found different risk estimates in MP models with both fine and coarse particles included).**

1 important fraction of PM_{10}. However, the Santiago, Chile study (Cifuentes et al., 2000) found

2 significant associations with both fine and coarse fractions and interesting seasonal differences,

3 as well. In Chock et al.'s (2000) analysis of Pittsburgh, PA data, the authors emphasized the lack

4 of significant PM associations; and no specific comments were made regarding the relative

5 importance of $PM_{2.5}$ versus $PM_{10-2.5}$.

6 The Canadian 8-city study (Burnett et al., 2000) is noteworthy for a variety of reasons,

7 including the use of elemental composition and principal components analyses to provide

8 additional information about the relative importance of fine and coarse particles. The $PM_{2.5}$

9 effect on mortality is greater than the $PM_{10-2.5}$ effect for all gaseous-pollutant models in Table 5 of

10 Burnett et al. (2000) and in the principal component model 1 in their Table 8, where both PM

11 size fractions and the four gaseous co-pollutants are used simultaneously. PM component

12 models from this study are discussed further below, in Section 8.2.2.4.2.

13 The Lippmann et al. (2000) results for Detroit are also noteworthy in that additional PM

14 indices were evaluated besides those depicted in Figure 8-6 and the overall results obtained may

15 be helpful in comparing fine- versus coarse-mode PM effects. In analyses of 1985 to 1990 data,

16 PM-mortality relative risks and their statistical significance were generally in descending order:

17 PM_{10}, $TSP-SO_4^=$, and $TSP-PM_{10}$. For the 1992-1994 period, relative risks for equivalent

18 distributional increment (e.g., IQR) were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for both

19 mortality and hospital admissions categories; and $SO_4^=$ was more strongly associated with most

20 outcomes than H^+. Consideration of the overall pattern of results led the authors to state that the

21 mass of the smaller size index could explain a substantial portion of the variation in the larger

22 size indices. In these data, on average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some

23 days) and PM_{10} for 66% of TSP mass. Also, the temporal correlation between TSP and $PM_{2.5}$

24 was r = 0.63, and for $PM_{2.5}$ vs. PM_{10} r = 0.90, suggesting that much of the apparent larger particle

25 effects may well be mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger

26 associations for sulfates than H^+, suggestive of non-acid fine particle effects, must be caveated by

27 noting the very low H^+ levels present (often circa non-detection limit).

28 Three research groups have examined the same Phoenix, AZ data set, using different

29 methods. While these groups used somewhat different approaches, there is some consistency

30 among their results in that $PM_{10-2.5}$ appeared to emerge as possibly the more important predictor

31 of mortality versus $PM_{2.5}$. In the Clyde et al. (2000) analysis, PM-mortality associations were

1   found only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the

2   association was with $PM_{10-2.5}$, not $PM_{2.5}$. Based on the Bayes Information Criterion, the highly

3   ranked models consistently included 1-day lagged $PM_{10-2.5}$. Smith et al.'s (2000) analyses found

4   that, based on a linear PM effect, $PM_{10-2.5}$ was significantly associated with total mortality, but

5    $PM_{2.5}$ was not. In the Mar et al. (2000) analysis, total mortality was significantly associated with

6   CO and NO_2 and weakly ($p < 0.1$) associated with PM_{10} and $PM_{10-2.5}$ (and $PM_{2.5}$ was more weakly

7   associated); however, cardiovascular mortality (CVM) was significantly associated with both

8    $PM_{2.5}$ and $PM_{10-2.5}$ at $p<0.05$. CVM was also significantly associated with a motor vehicle source

9   category with loading of $PM_{2.5}$, EC, OC, CO, NO_2, and some trace metals, as shown by factor

10   analyses discussed below. The $PM_{2.5}$ in Phoenix is mostly generated from motor vehicles,

11   whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles from natural (wind

12   blown dust) and anthropogenic (construction and road dust) processes, and (b) organic particles

13   from natural biogenic processes (endotoxin and molds) and anthropogenic (sewage aeration)

14   processes.

15   The Castillejos et al. (2000) and Cifuentes et al. (2000) analyses also appear to implicate

16   $PM_{10-2.5}$, as well as $PM_{2.5}$, as importantly contributing to mortality in two non-U.S. locations,

17   Mexico City and Santiago, Chile. The latter study also suggests possible seasonal differences in

18   Santiago, the PM effects in summer being more than double those in winter at that South

19   American location.

20

21   **Crustal Particle Effects**

22   Since the 1996 PM AQCD, several studies have yielded interesting new information

23   concerning possible roles of crustal wind-blown particles or crustal particles within the fine

24   particle fraction (i.e., $PM_{2.5}$) in contributing to observed PM-mortality effects.

25   Schwartz et al. (1999), for example, investigated the association of coarse particle

26   concentrations with non-accidental deaths in Spokane, Washington, where dust storms elevate

27   coarse particle concentrations. During the 1990-1997 period, 17 dust storm days were identified.

28   The PM_{10} levels during those storms averaged 263 $\mu g/m^3$, compared to 39 $\mu g/m^3$ for the entire

29   period. The coarse particle domination of PM_{10} data on those dust storm days was confirmed by

30   a separate measurement of PM_{10} and PM_1 during a dust storm in August, 1996: the PM_{10} level

31   was 187 $\mu g/m^3$, while PM_1 was only 9.5 $\mu g/m^3$. The deaths on the day of a dust storm were

1   contrasted with deaths on control days (n=95 days in the main analysis and 171 days in the

2   sensitivity analysis), which are defined as the same day of the year in other years when dust

3   storms did not occur. The relative risk for dust storm exposure was estimated using Poisson

4   regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity

5   analyses considering different seasonal adjustment, year effects, and lags, were conducted. The

6   expected relative risk for these storm days with an increment of 221 μg/m^3 would be about 1.04,

7   based on PM$_{10}$ relative risk from past studies, but the estimated RR for high PM$_{10}$ days was found

8   to be only 1.00 (95% CI=0.95-1.05) per 50 μg/m^3 PM$_{10}$ change in this study. Schwartz et al.

9   concluded that there was no evidence to suggest that coarse (presumably crustal) particles were

10   associated with daily mortality.

11   Pope et al. (1999a) investigated PM$_{10}$-mortality associations in three metropolitan areas

12   (Ogden, Salt Lake City, and Provo/Orem) in Utah's Wasatch Front mountain region during the

13   1985-1995 period. Although the three metropolitan areas shared common weather patterns,

14   pollution levels and patterns among the three areas were different due to different emission

15   sources. The authors utilized an index of air stagnation (the clearing index which the National

16   Weather Service computes from temperature, moisture and wind) to identify and screen obvious

17   windblown dust days, days clearly identified as with low stagnation index but high PM$_{10}$. They

18   found that Salt Lake City experienced substantially more episodes of wind-blown dust. They

19   therefore conducted Poisson regression of mortality series using both unscreened and screened

20   PM$_{10}$ data. The effects of screening were most apparent in Salt Lake City results. Before

21   screening, no significant relationships were observed; after screening, the RRs per 50 μg/m^3

22   increase in PM$_{10}$ for mortality in the three metropolitan areas were 1.12 (95% CI: 1.045 - 1.20),

23   1.023 (1.00 - 1.047), and 1.019 (0.979 - 1.06) for Ogden, Salt Lake City, and Provo/Orem,

24   respectively. These results suggest that the pollution episodes of wind-blown (crustal-derived)

25   dusts were less associated with mortality than were the episodes of (presumably) combustion-

26   related particles.

27   Ostro et al. (1999a) analyzed the Coachella Valley, CA data for 1989-1992. This desert

28   valley, where coarse particles of geologic origin comprise circa 50-60% of annual-average PM$_{10}$

29   (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and Indio,

30   CA. Total, respiratory, cardiovascular, non-cardiorespiratory and age-over-50 deaths were

31   analyzed. The correlation between gravimetric and beta-attenuation measurements, separated by

1	25 miles, was high (r = 0.93); and the beta-attenuation data were used for analysis. GAM
2	Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used.
3	Seasonally stratified analyses were also conducted. Lags 0 through 3 days (separately) of PM_{10},
4	along with moving averages of 3 and 5 days, were evaluated, as were O_3, NO_2, and CO.
5	Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined,
6	except non-cardiorespiratory. Effect size estimates for total and cardiovascular deaths were
7	larger for warm season (May through October) than for all year, analogous to the Cifuentes et al.
8	(2000) findings for Santiago, Chile. NO_2 and CO were statistically significant predictors of
9	mortality in single pollutant models; but in multi-pollutant models, all gaseous pollutants
10	coefficients were reduced and non-significant, whereas PM_{10} coefficients remained the same and
11	significant. Ostro et al. (2000) also conducted a follow-up study of the Coachella Valley data for
12	1989-1998, using actual $PM_{2.5}$ and $PM_{10-2.5}$ data for the last 2.5 years but $PM_{2.5}$ and $PM_{10-2.5}$
13	concentrations estimated for the other, earlier years. $PM_{2.5}$, CO, and NO_2 were significantly
14	associated with all-cause mortality; and PM_{10} and $PM_{10-2.5}$ with cardiovascular mortality, but not
15	$PM_{2.5}$ (possibly due to the low range of concentrations and reduced sample size for $PM_{2.5}$ data
16	versus PM_{10} data). Thus, although the cardiovascular mortality results hint at crustal particle
17	effects possibly being important in this desert situation, the ability to discern more clearly the
18	role of fine particles would likely be improved by analyses of more years of actual data for $PM_{2.5}$.
19	Laden et al. (2000) analyzed Harvard Six Cities study data and Mar et al. (2000) the
20	Phoenix data to investigate the role of crustal particles in $PM_{2.5}$ samples on daily mortality.
21	These studies are discussed in more detail below in Section 8.2.2.4.3 on the source-oriented
22	evaluation of PM; and only the basic results regarding crustal particles are mentioned here. The
23	elemental abundance data (from X-ray fluorescence spectroscopy analysis of daily filters) were
24	analyzed to estimate the concentration of crustal particles in $PM_{2.5}$ using factor analysis. Then
25	the association of mortality with fine crustal mass was estimated using Poisson regression
26	(regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather.
27	No positive association was found between fine crustal mass factor and mortality.
28	The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are
29	not likely associated with daily mortality. However, as noted in the previous section, three
30	analyses of Phoenix, AZ data suggested that $PM_{10-2.5}$ may be associated with mortality. The
31	results from one of the three studies (Smith et al., 2000) suggest that coarse particle mortality

1   associations are stronger in spring and summer, when the anthropogenic portion of $PM_{10-2.5}$ is

2   lowest as determined by factor analysis. However, during spring and summer, biogenic

3   processes (e.g., wind-blown endotoxins and molds) may contribute more to the $PM_{10-2.5}$ fraction

4   in the Phoenix area, clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles,

5   per se. Disentangling potential contributions of biogenically-derived organic particle

6   components from those of crustal materials in the $PM_{10-2.5}$ fraction in Mexico City and Santiago

7   poses further interesting challenges.

8

9   **Ultrafine Particle Effects**

10   The Wichmann et al. (2000) study evaluated the attribution of PM effects to specific size

11   fractions, including both the number concentration (NC) and mass concentration (MC) of

12   particles in a given size range.   The study was carried out in the small German city of Erfurt

13   (pop. 200,000) in the former German Democratic Republic, by a team of scientists at the

14   Gessellschaft fur Strahlenforschung (GSF) and Ludwig Maximilian University in Germany.

15   Erfurt was heavily polluted by particles and SO_2 in the 1980s, and excess mortality was attributed

16   to high levels of TSP by Spix et al. (1993). Concentrations of PM and SO_2 have markedly

17   dropped since then. The present study provides a much more detailed look at the health effects

18   of ultrafine particles (diameter < 0.1 μm) than earlier studies, and allows examination of effects

19   related to number counts for fine and ultrafine particles, as well as to their mass.

20   The Mobile Aerosol Spectrometer (MAS), developed by GSF, produces number and mass

21   concentrations in three size classes of ultrafines (0.01 to 0.1 μm) and three size classes of larger

22   fine particles (0.1 μm to 2.5 μm). The mass concentration MC0.01-2.5 is well correlated with

23   gravimetric $PM_{2.5}$, and the number concentration NC0.01-2.5 is well correlated with total particle

24   counts from a condensation particle counter (CPC). Mortality data were coded by cause of death,

25   with some discrimination between underlying causes and prevalent conditions of the deceased.

26   Some analyses looked at cardiovascular causes without respiratory, respiratory without

27   cardiovascular, and both causes together as separate groups. Age was used as a modifying factor,

28   as was weekly data for all of Germany on influenza and similar diseases. Daily mortality data

29   were fitted using a Poisson Generalized Additive Model (GAM), with adjustments for weather

30   variables, time trends, day of week, and particle indices. Two types of models were fitted, one

1   using the best single-day lag for air pollution and a second using the best polynomial distributed

2   lag (PDL) model for air pollution.

3   Winter PM generally had the most significant positive effects on mortality, and fall PM

4   effects were similar in magnitude, but less significant because of the smaller NC and MC in fall

5   than in winter. Summer PM effects were consistently lower and not significant. PDL models

6   generally had larger and more significant PM effects than single-day lag models. Log-

7   transformed pollution models occasionally provided better fits than untransformed pollutant

8   models, particularly for number concentration indices in single-day lag models. However, there

9   were some nonlinear relationships that could not be adequately described by either parametric

10   model, as shown by use of LOESS models. The results cited in Table 8-1 and Appendix

11   Table 8A-1 are all for linear PDL models, to facilitate comparison.

12   Mass concentration was most often significantly associated with excess mortality in

13   one-pollutant models, with excess risks for MAS MC$\underline{0.1\text{-}2.5}$ being about 6.2% (CI 1.4, 11.2) per

14   25 $\mu g/m^3$. The non-significant estimate from filter $PM_{2.5}$ was about 3% (CI -1.7, 7.9) per

15   25 $\mu g/m^3$. Filter PM_{10} estimates were also significant predictors of mortality overall, about 6.6%

16   excess risk per 50 $\mu g/m^3$ (CI 0.7 to 12.8) in PDL models.

17   Mass concentrations for smaller fine particles were also often significant, with excess risk

18   for MC$\underline{0.01\text{-}1.0}$ being ca. 5.1% (CI 0.2, 10.2) per 25 $\mu g/m^3$ in a linear PDL model. Smaller-size

19   components of MC$\underline{0.01\text{-}1.0}$ were also significantly associated, or nearly so, with excess

20   mortality. The intermodal fraction MC$\underline{1.0\text{-}2.5}$ was also significant in a PDL logarithmic model,

21   4.7% (CI 1.05, 8.5) per IQR in log concentration. No results were reported for the effects of

22   ultrafine mass concentrations in classes 0.01-0.03, 0.03-0.05, or 0.05-0.1 $\mu g/m^3$.

23   Number concentrations of ultrafine particles were also associated with excess mortality,

24   significantly or nearly so in smaller size classes. The results for linear models are shown in

25   Table 8-3. The table also shows how much the estimated excess risks are reduced, sometimes

26   drastically, when co-pollutants (especially SO_2 and NO_2) are included in a two-pollutant model.

27   Number and mass concentrations of various ultrafine and fine particles in all size ranges are

28   rather well correlated with gaseous co-pollutants except for the intermodal size range $\underline{MC1.0\text{-}2.5}$.

29   The correlations range from 0.44 to 0.62 with SO_2, from 0.58 to 0.66 with NO_2, and from 0.53 to

30   0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2, from 0.48 to 0.60 with

31   NO_2, and from 0.56 to 0.62 with CO. The large decreases in excess risk for number

**TABLE 8-3. EXCESS TOTAL MORTALITY RISKS ESTIMATED TO BE
ASSOCIATED WITH VARIOUS AMBIENT PARTICLE SIZE-RELATED INDICES**

PM Index	Co-Pollutant	Single-Pollutant Models		
		Excess Risk, %	Lower 95% CL	Upper 95% CL
NC<u>0.01-0.03</u>	None	3.00[a]	−0.342	6.455
NC0.<u>03-0.05</u>	None	3.80[a]	0.021	7.722
NC0.<u>05-0.1</u>	None	4.00[a]	−0.307	8.493
NC0.<u>01-2.5</u>	None	6.891[b]	0.662	13.504
NC<u>0.01-0.1</u>	None	8.238[b]	0.252	16.86
	SO$_2$	4.758[b]	−0.451	10.239
	NO$_2$	0.739[b]	−3.951	5.658
	CO	3.594[b]	−2.312	9.856
	MC<u>0.01-2.5</u>	4.123[b]	−1.437	9.996
MC<u>0.01-2.5</u>	None	6.194[c]	1.409	11.205
	SO$_2$	2.014[c]	−2.304	6.523

[a]Risks estimates for mortality associated with number concentrations (NC) in specified ranges. At actual
 interquartile range, respectively 8888, 2524, and 1525 particles/cm^3.
[b]At standard increment 25,000 particles/cm^3; winter IQR is 22,211 particles/cm^3, annual IQR is 12,690 particles/cm^3.
[c]At standard increment 25 μg/m^3.

Source: Based on Wichman et al. (2000), as calculated by U.S. EPA.

1   concentration, particularly when NO$_2$ is a co-pollutant with NC<u>0.01-0.1</u>, clearly involves a more

2   complex structure than simple correlation. The large decrease in excess risk when SO$_2$ is a

3   co-pollutant with MC<u>0.01-2.5</u> is not readily explained, and it is discussed in some detail in

4   Wichmann et al. (2000).

5   SO$_2$ is a strong predictor of excess mortality in this study; and its estimated effect is little

6   changed when different particle indicators are included in a two-pollutant model. The authors

7   noted: ". . .the [LOESS] smoothed dose response curve showed most of the association at the

8   left end, below 15 μg/m^3, a level at which effects were considered biologically implausible. . ."

9   Replacement of sulfur-rich surface coal has reduced mean SO$_2$ levels in Erfurt from 456 μg/m^3

10 in 1988 to 16.8 μg/m^3 during 1995 to 1998 and to 6 μg/m^3 in 1998. The estimated concentration-

11 response functions for SO$_2$ are very different in these time periods, comparing Spix et al. (1993)

1   with Wichmann et al. (2000) results. Wichmann et al. concluded "These inconsistent results for

2   SO_2 strongly suggested that SO_2 was not the causal agent but an indicator for something else."

3   The authors offered no specific suggestions as to what the "something else" might be, but they

4   did finally conclude that their studies from Germany strongly supported particulate air pollution

5   as more relevant than SO_2 to observed mortality impacts.

6   The authors also found that ultrafine particles, NO_2 and CO form a group of pollutants

7   strongly identified with motor vehicle traffic. Immediate and delayed effects seemed to be

8   independent in two-pollutant models, with single-day lags of 0 to 1 days and 4 to 5 days giving

9   'best fits' to data. The delayed effect of ultrafine particles was stronger than that for NO_2 or CO.

10   Another finding of interest is that the excess risk in Erfurt is larger and more significantly

11   associated with ages < 70 years than with older ages. This is consistent for PDL models for

12   NC0.01-0.1, MC0.01-2.5, and PM_{10}. None of the single lag day models were significant.

13   Examination of prevalent disease categories found larger and more significant risks for

14   respiratory disease mortality than for cardiovascular mortality in almost all models. Combined

15   cardiovascular or combined respiratory diseases were generally the next highest category. Other

16   natural causes (i.e., neither respiratory nor cardiovascular) almost always had the lowest risk.

17

18   *8.2.2.4.2 Chemical Components*

19   Ten new studies from the U.S. and Canada examined specific chemical components of PM.

20   Table 8-4 shows the chemical components examined in these studies, the mean concentrations

21   for Coefficient of Haze (COH), sulfate, and H^+, as well as the list of those that were found to be

22   associated with increased mortality. There are several chemical components of PM whose

23   associations with mortality can be compared across studies, including COH, sulfate, and H^+.

24

25   **Coefficient of Haze, Elemental Carbon, and Organic Carbon**

26   COH is highly correlated with elemental carbon (EC) and is often considered as a good PM

27   index for motor vehicle sources (especially diesel), although other combustion processes such as

28   space heating likely also contribute to COH levels. Several studies (Table 8-4) examined COH;

29   and, in most cases, positive and significant associations with mortality outcomes were reported.

30   In terms of relative significance of COH in comparison to other PM components, COH was not

31   the clearly most significant PM component in any of these studies. The average level of COH in

TABLE 8-4. SUMMARY OF PARTICULATE MATTER CHEMICAL COMPONENTS ANALYZED IN RECENT STUDIES

Author, City	Mean COH (1000ft)	Mean $SO_4^=$ ($\mu g/m^3$)	Mean H^+ ($nmol/m^3$)	Other PM components analyzed	PM components associated with mortality. Comments.
Burnett et al. (1998b) Toronto, Canada. 1980-1994.	0.42	9.2		TSP, estimated PM_{10} and $PM_{2.5}$	TSP, COH, sulfate, estimated PM_{10} and $PM_{2.5}$. However, CO together with TSP explained most of the association.
Burnett et al. (2000). 8 largest Canadian cities 1986-1996.	0.26	2.6		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and 47 trace elements	PM_{10}, $PM_{2.5}$, COH, sulfate, Zn, Ni, and Fe significantly associated with total mortality.
Fairley (1999). Santa Clara County, CA	0.5	1.8		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and nitrate	COH, sulfate, nitrate, PM_{10}, and $PM_{2.5}$ were associated with mortality. $PM_{2.5}$ and nitrate most significant.
Gwynn et al. (2000). Buffalo, NY 1988-1990	0.2	5.9	36.4	PM_{10}	Sulfate, H^+, PM_{10}, and COH were associated with total mortality. COH was least significant predictor.
Lipfert et al. (2000a). Philadelphia, PA 1992-1995	0.28	5.1	8.0	Nephelometry, NH_4^+, TSP, PM_{10} $PM_{2.5}$, and $PM_{10-2.5}$	Essentially all PM components were associated with mortality.
Lippmann et al. (2000). Detroit, MI 1992-1994		5.2	8.8	PM_{10} $PM_{2.5}$, and $PM_{10-2.5}$	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more strongly associated with mortality outcomes than sulfate or H^+.
Klemm and Mason (2000). Atlanta, GA 1998-1999		5.2	0	Nitrate, EC, OC, oxygenated HC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	"Interim" results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were: H^+, PM_{10}, and $PM_{2.5}$,

TABLE 8-4 (cont'd). SUMMARY OF PARTICULATE MATTER CHEMICAL COMPONENTS ANALYZED IN RECENT STUDIES

Author, City	Mean COH (1000ft)	Mean $SO_4^=$ (μg/m^3)	Mean H$^+$ (nmol/m^3)	Other PM components analyzed	PM components associated with mortality. Comments.
Mar et al. (2000). Phoenix, AZ 1995-1997				S, Zn, Pb, soil-corrected K, reconstructed soil, EC, OC, TC, PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$	S, Pb, and soil were negatively associated with total mortality. PM$_{10}$ and PM$_{10-2.5}$ were positively associated with total mortality. Soil-corrected K, non-soil PM$_{2.5}$, EC, OC, TC, PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ 1981-1983		12.7		PM$_{15}$, PM$_{2.5}$, sulfates cyclohexane-solubles (CX), dichloromethane-solubles (DCM), and acetone-solubles (ACE).	PM$_{15}$, PM$_{2.5}$, sulfate, CX and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek et al. (2000). The Netherlands 1986-1994		3.8 (median)		PM$_{10}$, BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than PM$_{10}$.
Goldberg et al. (2000). Montreal, Quebec, Canada. 1984-1993.	0.24	3.3		Predicted PM$_{2.5}$, and extinction coefficient (visual-range derived).	COH, predicted PM$_{2.5}$, and sulfate were associated with various mortality outcomes (mostly elderly and stronger associations in summer).
Anderson et al. (2001). The west Midlands conurbation, UK. 1994-1996.		3.7		PM$_{10}$, PM$_{2.5}$, PM$_{10-2.5}$, and BS.	Significant associations between all-cause mortality with PM indices (except PM$_{10-2.5}$) were seen only in warm season.

1   these studies ranged from 0.2 (Buffalo, NY) to 0.5 (Santa Clara County, CA) 1000 linear feet.

2   The correlations between COH and NO$_2$ or CO in these studies (8 largest Canadian cities; Santa

3   Clara County, CA; and Buffalo, NY) were moderately high (r ≈ 0.7 to 0.8), suggesting a likely

1   motor vehicle contribution. Some of the inconsistencies in the results across cities may be in

2   part, due to the differences in COH levels. For example, in Buffalo, NY (where COH was

3   lowest), no significant association was found for any pollutant, possibly due to small sample size

4   ($\approx$ 1 year of data). However, both EC and OC were significant predictors of cardiovascular

5   mortality in the Phoenix study, with their effect sizes per IQR being comparable to those for

6   PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$; there, EC and OC represented major mass fractions of $PM_{2.5}$ (11% and

7   38%, respectively) and correlated highly with $PM_{2.5}$ (r = 0.84 and 0.89, respectively). They were

8   also highly correlated with CO and NO_2 (r $\approx$ 0.8 to 0.9), indicating their associations with an

9   "automobile" factor. Thus, the COH and EC/OC results from the Mar et al. (2000) study suggest

10   that PM components from motor vehicle sources are likely associated with mortality.

11   In a recent study in Montreal, Quebec, by Goldberg et al. (2000), COH appeared to be

12   correlated with some of the mortality outcomes more strongly than other PM indices such as the

13   visual-range derived extinction coefficient (considered to be a good indicator of sulfate).

14   However, the main focus of the study was the role of cardio-respiratory risk factors for air

15   pollution, and the investigators warned against comparing the relative strength of associations

16   among PM indices, pointing out complications such as likely error involved in the visual range

17   measurements. Also, the estimated $PM_{2.5}$ values were predicted from other PM indices,

18   including COH and extinction coefficient, making it difficult to compare straightforwardly the

19   relative importance of PM indices.

20

21   **Sulfate and Hydrogen Ion**

22   Sulfate and H^+, markers of acidic components of PM, have been hypothesized to be

23   especially harmful components of PM (Lippmann and Thurston, 1996). The newly available

24   studies that examined sulfate are shown in Table 8-4; four of them also analyzed H^+ data. The

25   sulfate concentrations ranged from 1.8 $\mu g/m^3$ (Santa Clara County, CA) to 12.7 $\mu g/m^3$ (three NJ

26   cities). Aside from the west versus east coast contrast, the higher levels observed in Toronto and

27   the three NJ cities are likely due to their study period coverage of the early 1980's, when sulfate

28   levels were higher. Sulfate explained 25 to 30% of $PM_{2.5}$ mass in eastern U.S. and Canadian

29   cities, but it was only 14% of $PM_{2.5}$ mass in Santa Clara County, CA. The mean H^+ level in the

30   Buffalo, NY study (36.4 $nmol/m^3$) was much higher than the levels in Philadelphia, Detroit, or

31   Atlanta, in part because the Buffalo study covered the 1988 summer when summer-haze episodes

1 occurred. The H^+ levels measured in the other three cities were low, especially in Atlanta, GA

2 (where the mean concentration was reported to be 0.0 μg/m^3). Even the mean H^+ concentration

3 for Detroit, MI (the H^+ was actually measured in Windsor, a Canadian city a few miles from

4 downtown Detroit), 8.8 nmol/m^3, was low compared to the reported detection limit of

5 15.1 nmol/m^3 (Brook et al., 1997) for the measurement system used in the study. Note that the

6 corresponding detection limit for sulfate was 3.6 nmol/m^3 (or 0.34 μg/m^3) and the mean sulfate

7 level for Detroit was 54 nmol/m^3 (or 5.2 μg/m^3), so that the signal-to-noise ratio is expected to be

8 higher for sulfate than for H^+. Thus, the ambient levels and possible relative measurement errors

9 for these data should be considered in interpreting the results of the studies listed in Table 8-4.

10 Sulfate was a statistically significant (at $p \le 0.05$) predictor of mortality, at least in single

11 pollutant models, in: Toronto, CN; the 8 largest Canadian cities; Santa Clara County, CA;

12 Buffalo, NY; Philadelphia, PA; Newark, NJ; Camden, NJ; and Montreal, Quebec, but not in

13 Detroit, MI, Elizabeth, NJ, or Atlanta, GA. However, it should be noted that the relative

14 significance across the cities is influenced by the sample size (both the daily mean death counts

15 and number of days available), as well as the range of sulfate levels, and therefore should be

16 interpreted with caution. Figure 8-7 shows the excess risks ($\pm$ 95% CI) estimated per 5 μg/m^3

17 increase in 24-h sulfate reported in these studies, compared to the earlier Six Cities Study result.

18 The largest estimate was seen for Santa Clara County, CA, but the wide confidence band

19 (possibly due to the small variance of the sulfate, since its levels were low) should be taken into

20 account. Also, in the Santa Clara County analysis, the sulfate effect was eliminated once $PM_{2.5}$

21 was included in the model, perhaps being indicative of sulfate mainly serving as a surrogate for

22 fine particles in general there. In any case, more weight should be accorded to estimates from

23 other studies with narrower confidence bands. In the other studies, the effect size estimates

24 mostly ranged from about 1 to 4% per 5 μg/m^3 increase in 24-h sulfate.

25 The relative significance of sulfate and H^+ compared to other PM components varied from

26 city to city, as seen in Table 8-4. Because each study included different combinations of

27 co-pollutants that had different extents of correlation with sulfate and because multiple mortality

28 outcomes were analyzed, it is difficult to assess the overall importance of sulfate across the

29 available studies. However, it can generally be seen that the associations were stronger in cities

30 where the sulfate and H^+ levels were relatively high. For example, the Gwynn et al., 2000

31 finding for Buffalo, NY data that H^+ and sulfate were most significantly associated with total
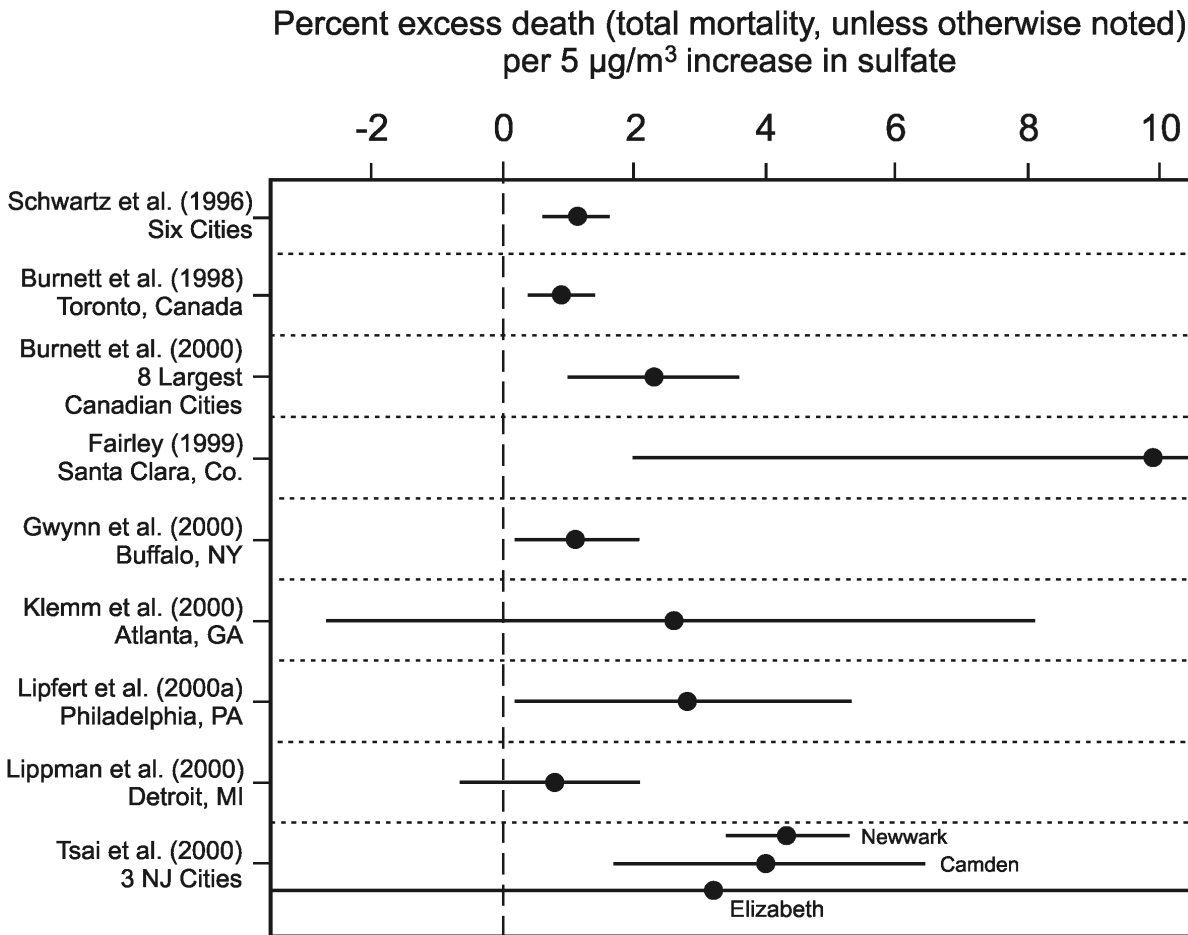
Figure 8-7. **Excess risks estimated for sulfate per 5 $\mu g/m^3$ increase from the studies in which both PM$_{2.5}$ and PM$_{10-2.5}$ data were available.**

1   mortality may be in part due to the high acid aerosol levels in that data. Also, the fact that the

2   Lippmann et al. (2000) finding for Detroit, MI data on H$^+$ and sulfate being less significantly

3   associated with mortality than the size-fractionated PM mass indices may be due to acidic

4   aerosols levels being mostly below the detection limit in that data. In this case, it appears that the

5   Detroit PM components show mortality effects even without much acidic input.

6   In summary, assessment of new study results for individual chemical components of PM

7   suggest that an array of PM components (mainly fine particle constituents) were associated with

8   mortality outcomes, including: COH, EC, OC, sulfate, H$^+$, and nitrate. The discrepancies seen

9   with regard to the relative significance of these PM components across studies may be in part due

1   to the difference in their concentrations. This issue is further discussed below as part of the

2   assessment of new studies involving source-oriented evaluation of PM components.

3

4   *8.2.2.4.3 Source-Oriented Evaluations*

5   Several new studies have conducted source-oriented evaluation of PM components.

6   In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous

7   co-pollutants were analyzed using factor analysis to estimate daily concentrations due to

8   underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear

9   combinations of associated individual variables. The mortality outcomes were then regressed on

10 those factors (factor scores) to estimate the impact of source types, rather than just individual

11 variables. These studies differ in terms of: specific objectives/focus, the size fractions from

12 which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The

13 main findings from these studies regarding the source-types identified (or suggested) and their

14 associations with mortality outcomes are summarized in Table 8-5.

15 The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 aimed to identify

16 distinct source-related fractions of $PM_{2.5}$ and to examine each fraction's association with

17 mortality. Fifteen elements in the fine fraction samples were routinely found above their

18 detection limits and included in the data analyses. For each of the six cities, up to 5 common

19 factors were identified from among the 15 elements, using specific rotation factor analysis.

20 Using the Procrustes rotation (a type of oblique rotation), the projection of the single tracer for

21 each factor was maximized. This specification of the tracer element was based on:

22 (1) knowledge from previous source apportionment research; (2) the condition that regression of

23 total fine mass on that element must result in a positive coefficient; and (3) identifications of

24 additional local source factors that positively contributed to total fine mass regression. Three

25 source factors were identified in all six cities: (1) a soil and crustal material factor with Si as a

26 tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and, (3) a coal combustion factor

27 with Se as a tracer. City-specific analyses also identified a fuel combustion factor (V), a salt

28 factor (Cl), and selected metal factors (Ni, Zn, or Mn). For each city, a GAM Poisson regression

29 model, adjusting for trend/season, day-of-week, and smooth function of temperature/dewpoint,

30 was used to estimate impacts of each source type (using absolute factor scores) simultaneously.

31 Summary estimates across cities were obtained by combining the city-specific estimates, using

TABLE 8-5. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PARTICULATE MATTER COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality. Comments.
Laden et. al., (2000) Harvard Six Cities 1979-1988	*Soil and crustal material*: Si *Motor vehicle emissions*: Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality associated with mobile source factor. Coal combustion factor was positively associated with mortality in all metropolitan areas, with exception of Topeka. Crustal factor from fine particles not associated with mortality. Coal and mobile sources account for majority of fine particles in each city.
Mar et al. (2000). Phoenix, AZ 1995-1997	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust*: Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and K_S (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S	$PM_{2.5}$ factors results: Soil factor and local SO_2 factor were negatively associated with total mortality. Regional sulfate was positively associated with total mortality on the same day, but negatively associated on the lag 3 day. Motor vehicle factor, vegetative burning factor, and regional sulfate factor were significantly positively associated with cardiovascular mortality.
	-- ***$PM_{10-2.5}$ (from dichot) trace elements:*** *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	Factors from dichot $PM_{10-2.5}$ trace elements not analyzed for associations with mortality because of small sample size (every-3rd day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions*: Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicles factors were associated with mortality.
Özkaynak et al. (1996). Toronto, Canada.	*Motor vehicle emissions*: CO, COH, and NO_2	Motor vehicle factor was a significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.

1   inverse variance weights. The identified factors and their tracers are listed in Table 8-5. The

2   results from mortality regression analysis including these factors indicated that the strongest

3   increase in daily mortality was associated with the mobile source factor. Also, the coal

4   combustion factor was positively associated with mortality in all metropolitan areas, except for

5   Topeka. Lastly, S, Ni, and Pb were specific elements individually associated with mortality, but

6   the crustal factor from fine particles was not.

7   Mar et al. (2000) analyzed PM_{10}, $PM_{10-2.5}$, two measurements of $PM_{2.5}$, and various

8   sub-components of $PM_{2.5}$ for their associations with total (non-accidental) and cardiovascular

9   deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor

10   analysis-derived factor scores. GAM Poisson models were used, adjusting for season,

11   temperature, and relative humidity. The evaluated air pollution variables included: O_3, SO_2,

12   NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-

13   corrected K (K_S), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. As earlier

14   noted, individual PM component results indicated that $PM_{10-2.5}$ was more significantly associated

15   with total mortality than $PM_{2.5}$, although both TEOM $PM_{2.5}$ and $PM_{10-2.5}$ were significantly

16   associated with cardiovascular mortality. A factor analysis conducted on the chemical

17   components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, K_S, OC, and EC) identified

18   factors for: motor vehicle emissions/re-suspended road dust; soil; vegetative burning; local SO_2

19   sources; and regional sulfate (see Table 8-5). The results of mortality regression with these

20   factors suggested that the soil factor and local SO_2 factor were negatively associated with total

21   mortality. Regional sulfate was positively associated with total mortality on the same day, but

22   negatively associated on the lag 3 day. The motor vehicle factor, vegetative burning factor, and

23   regional sulfate factor were each significantly positively associated with cardiovascular mortality.

24   The authors also analyzed elements from dichot $PM_{10-2.5}$ samples, and identified soil, a source of

25   coarse fraction metals (industry), and marine influence factors. However, these factors were not

26   analyzed for their associations with mortality outcomes due to the short measurement period

27   (starting in June 1996 with every-3rd-day sampling).

28   It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included

29   factor analysis on the elements from the coarse fraction and identified essentially the same

30   factors ("a source of coarse fraction metals" factor in Mar et al.'s study was called "the

31   anthropogenic elements" in Smith et al.'s study). While Smith et al. did not relate these factors

1   to mortality (due to a small sample size), they did show that the anthropogenic elements were

2   low in summer and spring, when the $PM_{10-2.5}$ effect was largest. These results suggest that the

3   $PM_{10-2.5}$ effects were not necessarily due to anthropogenic components of the coarse particles,

4   with biogenically-generated coarse particles perhaps being key during the warmer months (as

5   noted earlier above).

6   Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM

7   source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis -

8   Poisson regression techniques. During the three-year study period (1981-1983), extensive

9   chemical speciation data were available, including nine trace elements, sulfate, and particulate

10 organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory

11 mortality were analyzed. Tsai et al. first conducted a factor analysis of trace elements and

12 sulfate, identifying major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning

13 (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson

14 regression of mortality on these factors, they also used an alternative approach in which the

15 inhalable particle mass (IPM, $D_{50} < 15 \, \mu m$) was first regressed on the factor scores of each of the

16 source types to apportion the PM mass; and then the estimated daily PM mass for each source

17 type was included in Poisson regression, so that RR could be calculated per mass concentration

18 basis for each PM source type. They found that oil burning (V, Ni), various industrial sources

19 (Zn, Cd), motor vehicle (Pb, CO), and the secondary aerosols, as well as the individual PM

20 indices IPM, FPM ($D_{50} < 3.5 \, \mu m$), and sulfates, were all associated with total and/or

21 cardiorespiratory mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for

22 the source-oriented PM were higher (≈ 1.10) than those for individual PM indices (≈ 1.02).

23   Özkaynak et al. (1996) analyzed 21 years of mortality and air pollution data in Toronto,

24 Canada. In addition to the usual simultaneous inclusion of multiple pollutants in mortality

25 regressions, they also conducted a factor analysis of all the air pollution and weather variables,

26 including TSP, SO_2, COH, NO_2, O_3, CO, relative humidity and temperature. The factor with the

27 largest variance contribution ($\approx 50\%$) had the highest factor loadings for CO, COH, and NO_2,

28 which they considered to be representative of motor vehicle emissions, since this pollution

29 grouping was also consistent with the emission inventory information for that city. They then

30 regressed mortality on the factor scores (a linear combination of standardized scores for the

31 covariates), after filtering out seasonal cycles and adjusting for temperature and day-of-week

1 effects. The estimated impacts on mortality from motor vehicle pollution ranged from 1 to 6%,

2 depending on the outcomes.

3 In summary, these studies suggest that a number of source-types are associated with

4 mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative

5 burning. The crustal factor from fine particles was not associated with mortality in the Harvard

6 Six Cities data. In Phoenix data, where coarse particles were reported to be associated with

7 mortality, the associations between the factors related to coarse particles (soil, marine influence,

8 and anthropogenic elements) and mortality could not be evaluated due to the small sample size.

9 However, the soil (i.e., crustal) factor from fine particles in the Phoenix data was negatively

10 associated with mortality. Thus, although some unresolved issues remain (mainly due to the lack

11 of sufficient data), the source-oriented evaluation approach, using factor analysis, thus far seems

12 to implicate fine particles of anthropogenic origin as being most important (versus crustal

13 particles of geologic origin) in contributing to observed increased mortality risks.

14

15 **8.2.2.5 New Assessments of Cause-Specific Mortality**

16 Consistent with similar findings described in the 1996 PM AQCD, most of the newly

17 available studies summarized in Tables 8-1 and 8A-1 that examined non-accidental total,

18 circulatory, and respiratory mortality categories (e.g., Samet et al., 2000a,b; Dominici et al.,

19 2000a; Moolgavkar, 2000a; Gwynn et al., 2000; Lippmann et al., 2000; Ostro et al., 1999a;

20 Schwartz, 2000c) found significant PM associations with both cardiovascular and/or respiratory-

21 cause mortality. Several (e.g., Ostro et al., 1998; Fairley, 1999; Gwynn et al., 2000; Borja-

22 Aburto et al., 1997; Wordley et al., 1997; Borja-Aburto et al., 1998; Prescott et al., 1998;)

23 reported estimated PM effects that were generally higher for respiratory deaths than for

24 circulatory or total deaths. Once again, the NMMAPS results for U.S. cities are among those of

25 particular note here due to the large study size and the combined, pooled estimates derived for

26 various U.S. regions.

27 The Samet et al. (2000a,b) NMMAPS 90-cities analyses not only examined all-cause

28 mortality (excluding accidents), but also evaluated cardiovascular, respiratory, and other

29 remaining causes of deaths. Results were presented for all-cause, cardio-respiratory, and "other"

30 mortality for lag 0, 1, and 2 days. The investigators commented that, compared to the result for

31 cardio-respiratory deaths showing 3.5% (CI 1.0, 5.9) increase per 50 $\mu g/m^3$ PM_{10}, there was less

1   evidence for non-cardio-respiratory deaths. However, the estimates for "other" mortality, though

2   half those for cardio-respiratory mortality, were nevertheless positive, with fairly high posterior

3   probability (e.g., 0.84 at lag 0 day) that the overall effects were greater than 0 (estimated percent

4   excess "other" deaths being $\approx$ 1.3 per 50 μg/m^3 PM$_{10}$ at lag 0). Dominici et al. (2000a) evaluated

5   the 20 largest U. S. cities, a subset of the cities included in Samet et al.'s NMMAPS analyses.

6   The pattern of PM$_{10}$ effects on cardiovascular and respiratory mortality was similar to that

7   discussed earlier for total mortality, with lag day 1 showing the largest estimates. In this case,

8   the PM$_{10}$ effect in these analyses was smaller and weaker for "other" causes. Regional model

9   results suggested that PM$_{10}$ effects in the western U.S. were larger than in the eastern or southern

10   U.S. The PM coefficients were little affected by including gaseous pollutants in the model.

11   The Lippmann et al. (2000) analyses of cause-specific mortality in Detroit also evaluated

12   such mortality at various lags (0-3 days) in relation to several PM indices (PM$_{10}$, PM$_{2.5}$, PM$_{10-2.5}$,

13   sulfate, H$^+$) and various gaseous pollutants (O$_3$, SO$_2$, NO$_2$ and CO), with appropriate adjustment

14   for season, temperature, relative humidity, etc. Significant effects for both cardiovascular and

15   respiratory mortality were more consistently found for the first three PM indices than for H$^+$ or

16   sulfate. Effect size estimates tended to be highest for lag 1 day. It is notable here that, in the

17   Lippmann et al. (2000) analysis of Detroit mortality data, the "other" mortality category also

18   showed statistically significant effect size estimates. The authors noted, however, that the

19   "other" (non-circulatory and non-respiratory) mortality showed seasonal cycles and apparent

20   influenza peaks, suggesting that this series may have also been influenced by respiratory

21   contributing causes.

22   Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-

23   specific mortality across a broad range of lag (0-5 days) times. Moolgavkar reported that in

24   Poisson regression GAM analyses, controlling for temperature and relative humidity, varying

25   patterns of results were obtained for PM indices in evaluations of daily deaths related to

26   cardiovascular disease (CVD), cerebrovascular disease (CrD), and chronic obstructive lung

27   disease (COPD) in three large U.S. metropolitan areas. In Cook County (Chicago area), the

28   association of PM$_{10}$ with CVD mortality was statistically significant at a lag of 3 days based on a

29   single-pollutant analysis and remained significantly associated with CVD deaths with a 3-day lag

30   in two pollutant models including one or another of CO, NO$_2$, SO$_2$, or O$_3$. In joint analyses with

31   both O$_3$ and SO$_2$, however, the PM$_{10}$ association became markedly reduced and non-significant.

1   Also, in Los Angeles single-pollutant analyses, PM_{10} and $PM_{2.5}$ were significantly associated with

2   CVD mortality with lags of 2 and 1 days, respectively; but their coefficients were not robust to

3   inclusion of one or more gaseous pollutants. In Maricopa Co., AZ, PM_{10} coefficients were large

4   for several lags and significantly associated with CVD mortality lagged 1 day, as were each of

5   the gaseous pollutants tested (except O_3) at several different lag times; and PM_{10} coefficients

6   seemed to be robust in 2-pollutant models including PM_{10} and NO_2. As for cerebrovascular

7   disease, Moolgavkar (2000) reported that there was little evidence of association for PM with

8   CrD deaths at any lag in any of the three counties analyzed. With regard to COPD deaths, PM_{10}

9   was significantly associated with COPD mortality (lag 2 days) in Cook County.

10   Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the

11   12 APHEA European cities (APHEA1). Using Poisson autoregressive models adjusting for

12   trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated for

13   each city and "meta-analyses" of city-specific estimates were conducted. The pooled excess risk

14   estimates for cardiovascular mortality were 1.0% (0.3, 1.7) per 25 μg/m^3 increase in BS and 2.0%

15   (0.5, 3.0) per 50 μg/m^3 increase in SO_2 in western European cities. The pooled risk estimates for

16   respiratory mortality in the same cities were: 2.0% (0.8, 3.2) and 2.5% (1.5, 3.4) for BS and SO_2,

17   respectively. Also of note, Wichmann et al. (2000) found significant associations of elevated

18   cardiovascular and respiratory disease mortality with various fine (and ultrafine) particle indices

19   evaluated in Erfurt, Germany. "Other" natural causes (neither cardio- or respiratory-related)

20   almost always had the lowest risk in those models evaluating cause-specific mortality.

21   Seeking unique cause-specificity of effects associated with various pollutants has been

22   difficult because the "cause specific" categories examined are typically rather broad (usually

23   cardiovascular and respiratory) and overlap; also cardiovascular and respiratory conditions tend

24   to occur together. Examinations of more specific cardiovascular and respiratory sub-categories

25   may be necessary to test hypotheses about any specific mechanisms, but smaller sample sizes for

26   more specific sub-categories may make a meaningful analysis difficult. The study by Rossi et al.

27   (1999), however, examined associations between TSP and detailed cardio-vascular and

28   respiratory cause-specific mortality in Milan, Italy for a 9-year period (1980-1989). They found

29   significant associations for respiratory infections (11% increase per 100 μg/m^3 increase in TSP;

30   95%CI: 5, 17) and for heart failure (7%; 95%CI: 3, 11), both on the same day TSP. The

31   associations with myocardial infarction (10%; 95%CI: 3, 18) and COPD (12%; 95%CI: 6, 17)

1   were found for the average of 3 and 4 day TSP levels. They noted the difference in lags between

2   temperature effects (i.e., cold temp. at lag 1 day for respiratory infections; hot temp. at lag 0 for

3   heart failure and myocardial infarction) and air pollution (TSP) effects. The immediate hot

4   temperature effects and the lagged cold temperature effects for total and cardiovascular mortality

5   have been reported in past studies (e.g., Philadelphia, Chicago), but investigations of the

6   differences in lags of PM effects for specific cardiovascular or respiratory categories have rarely

7   been conducted in time-series mortality studies.

8   In the Hoek et al. (2001) study of the whole population of the Netherlands, the large sample

9   size (mean daily total deaths ~330, or more than twice that of Los Angeles County) allowed

10   examination of specific cardiovascular cause of deaths. Deaths due to heart failure, arrhythmia,

11   cerebrovascular causes, and thrombocytic causes were more strongly (~2.5 to 4 times larger

12   relative risks) associated with air pollution than the overall cardiovascular deaths. The

13   investigators concluded that specific cardiovascular causes (such as heart failure) were more

14   strongly associated with air pollution than total cardiovascular mortality, but noted that the

15   largest contribution to the association between air pollution and cardiovascular mortality was

16   from ischemic heart disease (about half of all cardiovascular deaths).

17   An HEI report on an epidemiologic study conducted by Goldberg et al. (2000) in Montreal,

18   Canada also provides interesting new information regarding types of medical conditions putting

19   susceptible individuals at increased risk for PM-associated mortality effects; and it highlights the

20   potential importance of evaluating "contributing causes" in cause-specific mortality analyses.

21   First, the immediate causes of death, as listed on death certificates, were evaluated in relation to

22   various ambient PM indices (TSP, PM_{10}, $PM_{2.5}$, COH, sulfates, extinction coefficients) lagged for

23   0 to 4 days, with results reported emphasizing effects at 3 day lags for three main PM measures

24   (COH, sulfate, estimated $PM_{2.5}$). Significant associations were observed between all three

25   measures and total nonaccidental deaths, respiratory diseases, and diabetes, with an approximate

26   2% increase in excess nonaccidental mortality being observed per 9.5 $\mu g/m^3$ interquartile

27   increase in 3-day mean estimated $PM_{2.5}$ exposure.

28   When underlying clinical conditions identified in decedents' medical records were then

29   evaluated in relation to ambient PM measures, all three measures (COH, sulfate, estimated $PM_{2.5}$)

30   were associated with acute lower respiratory disease, congestive heart failure, and any

31   cardiovascular disease. Estimated $PM_{2.5}$ and COH were also reported to be associated with

1   chronic coronary artery disease, any coronary artery disease, and cancer; whereas, sulfate was

2   associated with acute and chronic upper respiratory disease. None of the three PM measures

3   were related to airways disease, acute coronary artery disease, or hypertension. These results

4   both tend to support previous findings identifying individuals with preexisting cardiopulmonary

5   diseases as being at increased risk for ambient PM effects and appear to implicate another risk

6   factor, diabetes (which typically also involves cardiovascular complications as it progresses), as a

7   possible susceptibility condition putting individuals at increased risk for ambient PM effects.

8   Two recent studies (Gouveia and Fletcher, 2000; Conceição et al., 2001), both using data

9   from Sao Paulo, Brazil, examined child mortality (age under 5 years). The study periods for

10   these studies did not overlap (1991-1993 for Conceição and Fletcher study; 1994-1997 for

11   Conceição). Although Gouveia and Fletcher found significant associations between air pollution

12   and elderly mortality, they did not find statistically significant associations between air pollution

13   and child respiratory mortality (PM_{10} coefficient was negative and not significant). In the

14   Conceição et al. (2001) analysis, significant associations were found between child respiratory

15   mortality and CO, SO_2, and PM_{10} in single pollutant models, and coefficients for CO and SO_2

16   remained significant in the multiple-pollutant (apparently all pollutants together) model. The

17   reported PM_{10} coefficient in the single pollutant model corresponds to percent excess respiratory

18   death of 7.1% (95% CI: 1.1, 13.7) per 50 $\mu g/m^3$ increase in PM_{10}. However, it should be noted

19   that the average daily respiratory mortality counts for these studies were relatively small

20   (~2.4/day). With the modest length of observations (3 years for Gouveia and Fletcher study, and

21   4 years for Conceição et al.'s study), the statistical power of the data were likely less than

22   desirable. Thus, there have not been enough data to elucidate the range of short-term PM effects

23   on child (respiratory) mortality.

24   Overall, then, the above assessment of newly available information provides interesting

25   additional new information (beyond that in the 1996 PM AQCD) with regard to cause-specific

26   mortality related to ambient PM. That is, a growing number of studies continue to report

27   increased cardiovascular- and respiratory-related mortality risks as being significantly associated

28   with ambient PM measures at one or another varying lag times. When specific subcategory of

29   cardiovascular disease was examined in a large population (The Netherlands study by Hoek

30   et al.), some of the subcategories such as heart failure were more strongly associated with PM

31   and other pollutants than total cardiovascular mortality. Largest effects estimates are most

1   usually reported for 0-1 day lags (with some studies also now noting a second peak at 3-4 day

2   lags). A few of the newer studies also report associations of PM metrics with "other" (i.e.,

3   non-cardiorespiratory) causes, as well. However, at least some of these "other" associations may

4   also be due to seasonal cycles that include relationships to peaks in influenza epidemics that may

5   imply respiratory complications as a "contributing" cause to the "other" deaths. Or, the "other"

6   category may include sufficient numbers of deaths due to diabetes or other diseases which may

7   also involve cardiovascular complications as contributing causes. Varying degrees of robustness

8   of PM effects are seen in the newer studies, as typified by estimates in multiple pollutant models

9   containing gaseous co-pollutants; many show little effect of gaseous pollutant inclusion on

10   estimated PM effect sizes, some show larger reductions in PM effects to non-significant levels

11   upon such inclusion, and a growing number also report significant associations of cardiovascular

12   and respiratory effects with one or more gaseous co-pollutants. Thus, the newer studies both

13   further substantiate PM effects on cardiovascular- and respiratory-related mortality, while also

14   pointing toward possible significant contributions of gaseous pollutants to such cause-specific

15   mortality, as well. The magnitudes of the PM effect size estimates are consistent with the range

16   of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

17

18   **8.2.2.6 Salient Points Derived from Summarization of Studies of Short-Term Particulate**
19   **Matter Exposure Effects on Mortality**

20   The most salient key points to be extracted from the above discussion of newly available

21   information on short-term PM exposures relationships to mortality can be summarized as follow:

22

23   ***PM_{10} effects estimates***. Since the 1996 PM AQCD, thus far, there have been more than 80 new

24   time-series PM-mortality analyses published. Estimated mortality relative risks in these studies

25   are generally positive, statistically significant, and consistent with the previously reported

26   PM-mortality associations. Of particular importance are several studies which evaluated

27   multiple cities using consistent data analytical approaches. The NMMAPS analyses for the

28   largest 90 U.S. cities (Samet et al., 2000a,b), which are thought to probably provide the most

29   precise estimates for PM_{10} effects applicable to the U.S., derived a combined nationwide excess

30   risk estimate of about 2.3% increase in total (non-accidental) mortality per 50 $\mu g/m^3$ increase in

31   PM_{10}. The other multi-city analyses, as well as various single city analyses, also obtained PM_{10}

1   effect sizes generally in the range of 1.5 to 8.5% per 50 μg/m^3 increase in PM$_{10}$, consistent with

2   the range of statistically significant estimates given in the 1996 PM AQCD. However, more

3   geographic heterogeneity is evident among the newer multi-city study results than was the case

4   among the fewer studies assessed in the 1996 PM AQCD. In particular, in the NMMAPS

5   analysis of the 90 largest U.S. cities data, the risk estimates varied by U.S. geographic region,

6   with the estimate for the Northeast being the largest (4.6% per 50 μg/m^3 PM$_{10}$ increase). The

7   observed heterogeneity in the estimated PM risks across cities/regions could not be explained

8   with the city-specific explanatory variables, such as the mean levels of pollution and weather,

9   mortality rate, sociodemographic variables (e.g., median household income), urbanization, or

10   variables related to measurement error. Notable apparent heterogeneity was also seen among

11   effects estimates for PM (and SO$_2$) indices in the multi-city APHEA studies conducted in

12   European cities. In APHEA2, they found that several city-specific characteristics, such as NO$_2$

13   levels and warm climate, were important effect modifiers. The issue of heterogeneity of effects

14   estimates is discussed further below in Section 8.4.

15

16   ***Confounding and effect modification by other pollutants***. Numerous new short-term PM

17   exposure studies not only continue to report significant associations between various PM indices

18   and mortality, but also between gaseous pollutants (O$_3$, SO$_2$, NO$_2$, and CO) and mortality as well.

19   In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models

20   did not meaningfully affect the PM effect size estimates. This was the case for the NMMAPS 90

21   cities study with regard to the overall combined U.S. regional and nationwide risk estimates

22   derived for that study. The issue of confounding is discussed further in Section 8.4.

23

24   ***Fine and coarse particle effects***. Newly available studies provide generally statistically

25   significant PM$_{2.5}$ associations with mortality, with effect size estimates falling in the range

26   reported in the 1996 PM AQCD. New results from Germany appear to implicate both ultrafine

27   (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as being important

28   contributors to increased mortality risks. As to the relative importance of fine and coarse

29   particles, in the 1996 PM AQCD there was only one acute mortality study that examined this

30   issue. In that study, the authors suggested that fine particles (PM$_{2.5}$), but not coarse particles

31   (PM$_{10-2.5}$), were associated with daily mortality. Now, more than ten studies have analyzed both

1    $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality. While the results from some of these new

2   studies (e.g., Santa Clara County, CA analysis [Fairley, 1999] and the largest 8 Canadian cities

3   analysis [Burnett et al., 2000]) did suggest that $PM_{2.5}$ was more important than $PM_{10-2.5}$ in

4   predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses [Clyde et al., 2000;

5   Mar et al., 2000; Smith et al., 2000]; Mexico City and Santiago, Chile studies [Castillejos et al.,

6   2000; Cifuentes et al., 2000]) suggest that $PM_{10-2.5}$ may also be important in at least some

7   locations. Seasonal dependence of size-related PM component effects observed in some of the

8   studies complicates interpretations.

9

10   *Chemical components of PM*. Several new studies have examined the role of specific chemical

11   components of PM. The studies conducted in U.S. and Canadian cities showed mortality

12   associations with specific fine particle components of PM including H^+, sulfate, nitrate, as well

13   as COH, but their relative importance varied from city to city, likely depending on their levels

14   (e.g., no clear associations in those cities where H^+ and sulfate levels were very low, i.e., circa

15   non-detection limits). The results of several studies that investigated the role of crustal particles,

16   although somewhat mixed, do not appear overall to support associations between crustal particles

17   and mortality (see also the discussion of source-oriented evaluations presented below).

18

19   *Source-oriented evaluations*. Several studies conducted source-oriented evaluations of PM

20   components using factor analysis. The results from these studies generally indicate that several

21   combustion-related source-types are likely associated with mortality, including: motor vehicle

22   emissions; coal combustion; oil burning; and vegetative burning. The crustal factor from fine

23   particles was not associated with mortality in the Harvard Six Cities data, and the soil (i.e.,

24   crustal) factor from fine particles in the Phoenix data was negatively associated with mortality.

25   Thus, the source-oriented evaluations seem to implicate fine particles of anthropogenic origin as

26   being most important as contributing to increased mortality and generally do not support

27   increased mortality risks being related to short-term exposures to crustal materials in U.S.

28   ambient environments examined to date.

29

30   *Cause-specific mortality.* Findings for new results concerning cause-specific mortality comport

31   well with those for total (non-accidental) mortality, the former showing generally larger effect

1   size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess risks

2   than for total mortality risks. An analysis of specific cardiovascular causes in a large population

3   (The Netherlands) suggested the specific causes of deaths such as heart failure was more strongly

4   associated with PM (and other pollutants) than total cardiovascular mortality.

5

6   *Lags.* In general, maximum effect sizes for total mortality appear to be obtained with 0-1 day

7   lags, with some studies finding a second peak for 3-4 days lags. There is also some evidence

8   that, if effects distributed over multiple lag days are considered, the effect size may be larger than

9   for any single maximum effect size lag day. Lags are discussed further in Section 8.4.

10

11   *Threshold*. Few new short-term mortality studies explicitly address the issue of thresholds. One

12   study that analyzed Phoenix, AZ data (Smith et al., 2000) did report some limited evidence

13   suggestive of a possible threshold for $PM_{2.5}$ there. However, several different analyses of larger

14   PM_{10} data sets across multiple cities (Dominici, et al., 2002; Daniels et al., 2000) generally

15   provide little or no support to indicate a threshold for PM_{10} mortality effects. Threshold issues

16   are discussed further in Section 8.4.

17

18   ## 8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate
19   Matter

20   **8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document**

21   *8.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies*

22   Mortality effects associated with chronic, long-term exposure to ambient PM have been

23   assessed in cross-sectional studies and, more recently, in prospective cohort studies. A number

24   of older cross-sectional studies from the 1970s provided indications of increased mortality

25   associated with chronic (annual average) exposures to ambient PM, especially with respect to

26   fine mass or sulfate ($SO_4^=$) concentrations. However, questions unresolved at that time regarding

27   the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette

28   smoking, economic status, etc.) across cities tended to limit the degree of confidence that was

29   placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) on such purely

30   "ecological" studies or on quantitative estimates of PM effects derived from these studies.

31   Evidence comparing the toxicities of specific PM components was relatively limited. The sulfate

1   and acid components had already been discussed in detail in the previous PM AQCD (U.S.

2   Environmental Protection Agency, 1986).

3

4   *8.2.3.1.2 Semi-Individual (Prospective Cohort) Chronic Exposure Studies*

5   Semi-individual cohort studies using subject-specific information about relevant covariates

6   (such as cigarette smoking, occupation, etc.) have provided more certain findings of long-term

7   PM exposure effects than past purely "ecological studies" (Künzli and Tager, 1997). At the same

8   time, these better designed cohort studies have largely confirmed the magnitude of PM effect

9   estimates from past cross-sectional study results.

10   Prospective cohort semi-individual studies of mortality associated with chronic exposures

11   to air pollution of outdoor origins have yielded especially valuable insights into the adverse

12   health effects of long-term PM exposures. The extensive Harvard Six-Cities Study (Dockery

13   et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their

14   findings of statistically significant positive associations between fine particles and excess

15   mortality, although the ACS study did not evaluate the possible contributions of other air

16   pollutants. Neither study considered multi-pollutant models, although the Six-City study did

17   examine various gaseous and particulate matter indices (including total particles, $PM_{2.5}$, $SO_4^=$, H^+,

18   SO_2, and ozone), finding that sulfate and $PM_{2.5}$ fine particles were best associated with mortality.

19   The excess RR estimates for total mortality in the Six-Cities study (and 95 percent confidence

20   intervals, CI) per increments in PM indicator levels were: Excess RR=15% (CI=6.1%, 32%) for

21   20 $\mu g/m^3$ PM_{10}; excess RR=11.4% (CI=4.3%, 23%)for 10 $\mu g/m^3$ $PM_{2.5}$; and excess RR=13.4%

22   (CI=5.1%, 29%) for 5 $\mu g/m^3$ $SO_4^=$. The estimates for total mortality derived from the ACS study

23   were excess RR=6.5% (CI=3.5%, 9.7%) for 10 $\mu g/m^3$ $PM_{2.5}$ and excess RR 3.5% (CI=1.9%,

24   5.1%) for 5 $\mu g/m^3$ $SO_4^=$. The ACS pollutant RR estimates were smaller than those from the

25   Six-Cities study, although their 95% confidence intervals overlap. In some cases in these studies,

26   the life-long cumulative exposure of the study cohorts included distinctly higher past PM

27   exposures, especially in cities with historically higher PM levels (e.g., Steubenville, OH); but

28   more current PM measurements were used to estimate the chronic PM exposures. In the ACS

29   study, the pollutant exposure estimates were based on concentrations at the start of the study

30   (during 1979-1983). Also, the average age of the ACS cohort was 56, which could overestimate

31   the pollutant RR estimates and perhaps underestimate the life-shortening associated with PM

1   associated mortality. Still, although caution must be exercised regarding the use of the reported

2   quantitative risk estimates, the Six-Cities and ACS semi-individual studies provided consistent

3   evidence of a significant mortality association with long-term exposure to PM of ambient origins.

4   In contrast to the Six-Cities and ACS studies, early results reported by Abbey et al. (1991)

5   and Abbey et al. (1995a) from the Adventist Health Study on Smog (AHSMOG) found no

6   significant mortality effects of previous PM exposure in a relatively young cohort of California

7   nonsmokers. However, these analyses used TSP as the PM exposure metric, rather than more

8   health relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study,

9   and considered a shorter follow-up time than the Six-Cities study (ten years vs. 15 years for the

10   Six-Cities study). Moreover, the AHSMOG study included only non-smokers, indicated by the

11   Six-Cities Study as having lower pollutant RR's than smokers, suggesting that a longer follow-up

12   time than considered in the past (10 years) might be required to have sufficient power to detect

13   significant pollution effects than is required in studies that include smokers (such as the

14   Six-Cities and ACS studies). Thus, greater emphasis has been placed thus far on the Six-Cities

15   and ACS studies.

16   Overall, the previously available chronic PM exposure studies collectively indicated that

17   increases in mortality are associated with long-term exposure to ambient airborne particles.

18   Also, effect size estimates for total mortality associated with chronic PM exposure indices

19   appeared to be much larger than those reported from daily mortality PM studies. This suggested

20   that a major fraction of the reported mortality relative risk estimates associated with chronic PM

21   exposure likely reflects cumulative PM impacts above and beyond those exerted by the sum of

22   acute exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM

23   AQCD (Chapter 12) reached several conclusions concerning four key questions about the

24   prospective cohort studies, as noted below:

25

26   (1) Have potentially important confounding variables been omitted?

27   "While it is not likely that the prospective cohort studies have overlooked plausible

28   confounding factors that can account for the large effects attributed to air pollution, there

29   may be some further adjustments in the estimated magnitude of these effects as individual

30   and community risk factors are included in the analyses." These include individual

31   variables such as education, occupational exposure to dust and fumes, and physical activity,

1   as well as ecological (community) variables such as regional location, migration, and

2   income distribution. Further refinement of the effects of smoking status may also prove

3   useful."

4

5   (2) Can the most important pollutant species be identified?

6   "The issue of confounding with co-pollutants has not been resolved for the

7   prospective cohort studies . . . Analytical strategies that could have allowed greater

8   separation of air pollutant effects have not yet been applied to the prospective cohort

9   studies." The ability to separate the effects of different pollutants, each measured as a long-

10 term average on a community basis, was clearly most limited in the Six Cities study. The

11 ACS study offered a much larger number of cities, but did not examine differences

12 attributable to the spatial and temporal differences in the mix of particles and gaseous

13 pollutants across the cities. The AHSMOG study constructed time- and location-dependent

14 pollution metrics for most of its participants that might have allowed such analyses, but no

15 results were reported.

16

17 (3) Can the time scales for long-term exposure effects be evaluated?

18   "Careful review of the published studies indicated a lack of attention to this issue.

19 Long-term mortality studies have the potential to infer temporal relationships based on

20 characterization of changes in pollution levels over time. This potential was greater in the

21 Six Cities and AHSMOG studies because of the greater length of the historical air pollution

22 data for the cohort [and the availability of air pollution data throughout the study]. The

23 chronic exposure studies, taken together, suggest that there may be increases in mortality in

24 disease categories that are consistent with long-term exposure to airborne particles, and that

25 at least some fraction of these deaths are likely to occur between acute exposure episodes.

26 If this interpretation is correct, then at least some individuals may experience some years of

27 reduction of life as a consequence of PM exposure."

28

29 (4) Is it possible to identify pollutant thresholds that might be helpful in health

30 assessments?

1   "Model specification searches for thresholds have not been reported for prospective

2   cohort studies. . . .   Measurement error in pollution variables also complicates the search

3   for potential threshold effects. . . .   The problems that complicate threshold detection in the

4   population-based studies have a somewhat different character for the long-term studies."

5

6 **8.2.3.2   Prospective Cohort Analyses of Chronic Particulate Matter Exposure Mortality**
7 **Effects Published Since the 1996 Particulate Matter Air Quality Criteria Document**

8   Considerable progress has been made towards addressing further the above issues.

9 For example, extensive reanalyses (Krewski et al., 2000) of the Six-Cities and ACS Studies,

10 conducted under sponsorship by the Health Effects Institute (HEI), indicate that the published

11 findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on

12 substantially valid data sets and statistical analyses. The HEI reanalysis project has demonstrated

13 that small corrections in input data have very little effect on the findings and that alternative

14 model specifications further substantiate the robustness of the originally reported findings.

15 In addition, some of the above key questions have been further investigated by Krewski et al.

16 (2000) via sensitivity analyses (in effect, new analyses) for the Six City and ACS studies data

17 sets, including consideration of a much wider range of confounding variables. Newly published

18 analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiate

19 original findings and, also, provide much clearer, stronger evidence for ambient PM exposure

20 relationships with increased lung cancer risk. Recently published analyses of AHSMOG data

21 (Abbey et al., 1999; Beeson et al., 1998) also extend the ASHMOG findings and show some

22 analytic outcomes different from earlier analyses reported out from the study. Results from the

23 Veterans' Administration- Washington University (hereafter called "VA") prospective cohort

24 study are now available (Lipfert et al., 2000). Still other, additional new studies suggestive of

25 possible effects of sub-chronic PM exposures on infant mortality (Woodruff et al., 1997; Bobak

26 and Leon, 1998; Lipfert, 2000; Chen et al., 2002) are also discussed below.

27

28 *8.2.3.2.1   Health Effects Institute Reanalyses of the Six-Cities and ACS Studies*

29   The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to

30 conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al.,

31 1993) and ACS (Pope et al., 1995) Studies of air pollution and mortality. The following

1   description of approach, key results, and conclusions is largely extracted from the Executive

2   Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort

3   was approached in two steps:

- Part I: Replication and Validation. The Reanalysis Team sought to test: (a) if the
  original studies could be replicated via a quality assurance audit of a sample of the
  original data and; (b) if the original numeric results could be validated.
- Part II: Sensitivity Analyses. The Reanalysis Team tested the robustness of the original
  analyses to alternate risk models and analytic approaches.

9   The Part I audit of the study population data for both the Six Cities and ACS Studies and of

10 the air quality data in the Six Cities Study revealed the data to be of generally high quality with

11 few exceptions. In both studies, a few errors were found in the data coding for and exclusion of

12 certain subjects; when those subjects were included in the analyses, they did not materially

13 change the results from those originally reported. Because the air quality data used in the ACS

14 Study could not be audited, a separate air quality database was constructed for the sensitivity

15 analyses in Part II.

16   The Reanalysis Team was able to replicate the original results for both studies using the

17 same data and statistical methods as used by the Original Investigators. The Reanalysis Team

18 confirmed the original point estimates, as shown in Table 8-6. For the Six Cities Study, they

19 reported the relative risk of mortality from all causes associated with an increase in fine particles

20 of 20.0 μg/m^3 as 1.28, the same as the 1.28 per 20 μg/m^3 reported by the Original Investigators.

21 For the ACS Study, the relative risk of all-cause mortality associated with a 20 μg/m^3 increase in

22 fine particles was 1.19 in the reanalysis, close to the original 1.14 value.

23   The Part II sensitivity analysis applied an array of different models and variables to

24 determine whether the original results would remain robust to different analytic assumptions and

25 model specifications. The Reanalysis Team first applied the standard Cox model used by the

26 Original Investigators and included variables in the model for which data were available from

27 both original studies, but had not been used in the published analyses (e.g. physical activity, lung

28 function, marital status). The Reanalysis Team also designed models to include interactions

29 between variables. None of these alternative models produced results that materially altered the

30 original findings.

31

TABLE 8-6. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM[a]	
		Total mortality Excess Relative Risk (95% CI)	Cardiopulmonary mortality Excess Relative Risk (95% CI)
Original Investigators' Findings			
Six City[b]	$PM_{2.5}$	*13% (4.4%, 23%)*	*17% (5.8%, 42%)*
Six City[b]	$PM_{15/10}$	*18% (6%, 32%)*	*e*
ACS Study[c]	$PM_{2.5}$	*6.8% (3.4%, 10%)*	*11.8% (6.8%, 17%)*
HEI reanalysis Phase I: Replication			
Six City Reanalysis[d]	$PM_{2.5}$	*11.3% (3%, 23%)*	*18.7% (6.3%, 33%)*
	PM_{15}	*18% (6%, 34%)*	*20% (2%, 41%)*
ACS Study Reanalysis[d]	$PM_{2.5}$	*9.1% (3.9%, 14.5%)*	*15.3% (9.1%, 21%)*
	PM_{15} *(dichot)*	*4% (1%, 7%)*	*7% (2%, 12%)*
	PM_{15} *(SSI)*	*2% (−1%, 4%)*	*6% (3%, 9%)*

[a] *Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, scaled to increments of 20 $\mu g/m^3$ increase for PM_{10}, and 10 $\mu g/m^3$ increments for PM_{15} and $PM_{2.5}$.*
[b] *Dockery et al. (1993).*
[c] *Pope et al. (1995).*
[d] *Krewski et al. (2000).*
[e] *Data presented only by smoking subgroup.*

1   Next, for both the Six Cities and ACS Studies, the Reanalysis Team investigated the

2   possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the

3   population. These analyses did not find differences in PM-mortality associations among

4   subgroups based on various personal characteristics (e.g., including gender, smoking status,

5   exposure to occupational dusts and fumes, and marital status). However, estimated effects of

6   fine particles did vary with educational level; the association between an increase in fine particles

7   and mortality tended to be higher for individuals without a high school education than for those

8   with more education. The Reanalysis Team postulated that this finding could be attributable to

9   some unidentified socioeconomic effect modifier. The authors concluded, "The Reanalysis

10   Team found little evidence that questionnaire variables had led to confounding in either study,

11   thereby strengthening the conclusion that the observed association between fine particle air

12   pollution and mortality was not the result of a critical covariate that had been neglected by the

13   Original Investigators." (Krewski et al., 2000, pp. 219-220).

1   In the ACS study, the Reanalysis Team tested whether the relationship between ambient

2   concentrations and mortality was linear. They found some indications of both linear and

3   nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes

4   of the concentration-response relationships warrant additional research in the future.

5   One of the criticisms of both original studies has been that neither analyzed the effects of

6   change in pollutant levels over time. In the Six Cities Study, for which such data were available,

7   the Reanalysis Team tested whether effect estimates changed when certain key risk factors

8   (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the

9   reanalysis results did not change when smoking and body mass index were allowed to vary over

10   time. The Reanalysis Team did find for the Six Cities Study, however, that when the general

11   decline in fine particle levels over the monitoring period was included as a time-dependent

12   variable, the association between fine particles and all-cause mortality was reduced (Excess

13   RR = 10.4%, [1.5%, 20%]). This would be expected, since the most polluted cities would be

14   expected to have the greatest decline as pollution controls were applied. Despite this adjustment,

15   the $PM_{2.5}$ effect estimate continued to be positive and statistically significant.

16   To test the validity of the original ACS air quality data, the Reanalysis Team constructed

17   and applied its own air quality dataset from available historical data. In particular, sulfate levels

18   with and without adjustment were found to differ by about 10% for the Six Cities Study. Both the

19   original ACS Study air quality data and the newly constructed dataset contained sulfate levels

20   inflated by approximately 50% due to artifactual sulfate. For the Six Cities Study, the relative

21   risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS

22   Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from

23   all causes and cardiopulmonary disease compared with unadjusted data, while the relative risk of

24   mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis

25   Team found essentially the same results as the original Harvard Six-Cities and ACS studies, even

26   after using independently developed pollution datasets and after adjusting for sulfate artifact.

27   Because of the limited statistical power to conduct most model specification sensitivity

28   analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity

29   analyses using only the ACS Study dataset that considered 151 cities. When a range of city-level

30   (ecologic) variables (e.g., population change, measures of income, maximum temperature,

31   number of hospital beds, water hardness) were included in the analyses, the results generally did

1   not change. The only exception was that associations with fine particles and sulfate were

2   reduced when city-level measures of population change or SO_2 were included in the model.

3   A major product of the Reanalysis Project is the determination that both pollutant variables

4   and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and

5   modeled correctly, spatial correlation could cause substantial errors in both the regression

6   coefficients and their standard errors. The Reanalysis Team identified several methods for

7   addressing this, each of which resulted in some reduction in the estimated regression coefficients.

8   The full implications and interpretations of spatial correlations in these analyses have not been

9   resolved, and were noted to be an important subject for future research.

10   When the Reanalysis Team sought to take into account both the underlying variation from

11   city to city (random effects) and variation from the spatial correlation between cities, associations

12   were still found between mortality and sulfates or fine particles. Results of various models, using

13   alternative methods to address spatial autocorrelation and including different ecologic covariates,

14   found fine particle-mortality associations that ranged from 1.11 to 1.29 (RR reported by original

15   investigators was 1.17) per 24.5 $\mu g/m^3$ increase in $PM_{2.5}$. With the exception of SO_2,

16   consideration of other pollutants in these models did not alter the associations found with

17   sulfates. The authors reported associations that were stronger for SO_2 than for sulfate, which

18   may indicate that the sulfate with artifact was "picking up" some of the SO_2 association, perhaps

19   because the artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977).

20   It should be recognized that the Reanalysis Team did not use data adjusted for artifactual sulfate

21   for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality

22   from all causes and cardiopulmonary disease increased. This result suggests that more analyses

23   with adjusted sulfate might result in somewhat higher relative risks associated with sulfate. The

24   Reanalysis Team concluded: "it suggests that uncontrolled spatial autocorrelation accounts for

25   24% to 64% of the observed relation. Nonetheless, all our models continued to show an

26   association between elevated risks of mortality and exposure to airborne sulfate" (Krewski et al.,

27   2000, p. 230).

28   In summary, the reanalyses generally confirmed the original investigator's findings of

29   associations between mortality and long-term exposure to PM, while recognizing that increased

30   mortality may be attributable to more than one ambient air pollution component. Regarding the

31   validity of the published Harvard Six-Cities and ACS Studies, the HEI Reanalysis Report

1   concluded that: "Overall, the reanalyses assured the quality of the original data, replicated the

2   original results, and tested those results against alternative risk models and analytic approaches

3   without substantively altering the original findings of an association between indicators of

4   particulate matter air pollution and mortality."

5

6   *8.2.3.2.2 The Extension of the ACS Study*

7   A very recent publication by Pope et al. (2002) extends the analyses (Pope et al., 1995) and

8   reanalyses (Krewski et al., 2000) of the ACS CPS-II cohort to an additional eight years of follow-

9   up. The new study has a number of advantages over the previous analyses, in that it: (a) doubles

10   the follow-up time from eight years to sixteen years, and triples the number of deaths;

11   (b) expands the ambient air pollution data substantially, including two recent years of fine

12   particle data, and adds data on gaseous co-pollutants; (c) improves statistical adjustments for

13   occupational exposure; (d) incorporates data on dietary covariates believed to be important

14   factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit,

15   and high-fiber grains; and (e) uses recent developments in non-parametric spatial smoothing and

16   random effects statistical models as input to the Cox proportional hazards model. Each

17   participant was identified with a specific metropolitan area, and mean pollutant concentrations

18   were calculated for all metropolitan areas with ambient air monitors in the one to two years prior

19   to enrollment. Ambient pollution during the follow-up period was extracted from the AIRS data

20   base. Averages of daily averages of the gaseous pollutants were used except for ozone, where

21   the average daily 1-hour maximum was calculated for the whole year and for the typical peak

22   ozone quarter (July, August, September). Mean sulfate concentrations for 1990 were calculated

23   from archived filters using quartz filters, virtually eliminating the historical sulfate artifact

24   leading to overestimation of sulfate concentrations.

25   The Krewski et al. (2000), Burnett et al. (2001a), and Pope et al. (2002) studies were

26   concerned that survival times of participants in nearby locations might not be independent of

27   each other, due to missing, unmeasured or mis-measured risk factors or their surrogates that may

28   be spatially correlated with air pollution, thus violating an important assumption of the Cox

29   proportional hazards model. Model fitting proceeded in two stages, the first of which was an

30   adjusted relative risk model with a standard Cox proportional hazards model including

31   individual-specific covariates and indicator variables for each metropolitan area, but not air

1   pollutants. In the second stage, the adjusted log(relative risks) were fitted to fine particle

2   concentrations or other air pollutants by a random effects linear regression model.

3   Models were estimated separately for each of four mortality (total, cardiopulmonary, lung

4   cancer, and causes other than cardiopulmonary or lung cancer deaths) endpoints for the entire

5   follow-up period, and for fine particles in three time periods (1979-1983, 1999-2000, and the

6   average of the mean concentrations in these two periods). The results are shown in Table 8-7.

7   Figures 8-8, 8-9, and 8-10 show the results displayed in Figures 2, 3, and 5 in Pope et al. (2002).

8   Figure 8-8 shows that a smooth non-parametric model can be reasonably approximated by a

9   linear model for all-cause mortality, cardiopulmonary mortality, and other mortality; but the

10 log(relative risk) model for lung cancer appears to be non-linear, with a steep linear slope up to

11 an annual mean concentration of about 13 μg/m^3 and a flatter linear slope at fine particle

12 concentrations > 13 μg/m^3.

13

14

TABLE 8-7. SUMMARY OF RESULTS FROM THE EXTENDED ACS STUDY[*]

Cause of death	PM$_{2.5}$, average over 1979-1983	PM$_{2.5}$, average over 1999-2000	PM$_{2.5}$, average over all seven years
All causes	4.1% (0.8, 7.5%)	5.9% (2.0, 9.9%)	6.2% (1.6, 11.0%)
Cardiopulmonary	5.9% (1.5, 10.5%)	7.9% (2.3, 14.0%)	9.3% (3.3, 15.8%)
Lung cancer	8.2% (1.1, 15.8%)	12.7% (4.1, 21.9%)	13.5% (4.4, 23.4%)
Other	0.8% (−3.0, 4.8%)	0.9% (−3.4, 5.5%)	0.5% (−4.8, 6.1%)

[*]Adjusted mortality excess risk ratios (95% confidence limits) per 10 μg/m^3 PM$_{2.5}$ by cause of death associated with each of the multi-year averages of fine particle concentrations. The multi-year average concentrations are used as predictors of cause-specific mortality for all of the 16 years (1982-1998) of the ACS follow-up study. The excess risk ratios are obtained from the baseline random effects Cox proportional hazards models adjusted for age, gender, race, smoking, education, marital status, BMI, alcohol consumption, occupational dust exposure, and diet. Based on Table 2 in Pope et al. (2002) and more precise data from authors (G. Thurston, personal communication, March 13. 2002).

1   Figure 4 in Pope et al. (2000) shows results of the stratified first-stage models: ages

2   < 60 and > 69 yr are marginally significant for total mortality; ages ≥ 70 are significant for

3   cardiopulmonary mortality; and ages 60-69 for lung cancer mortality. Men are at significantly
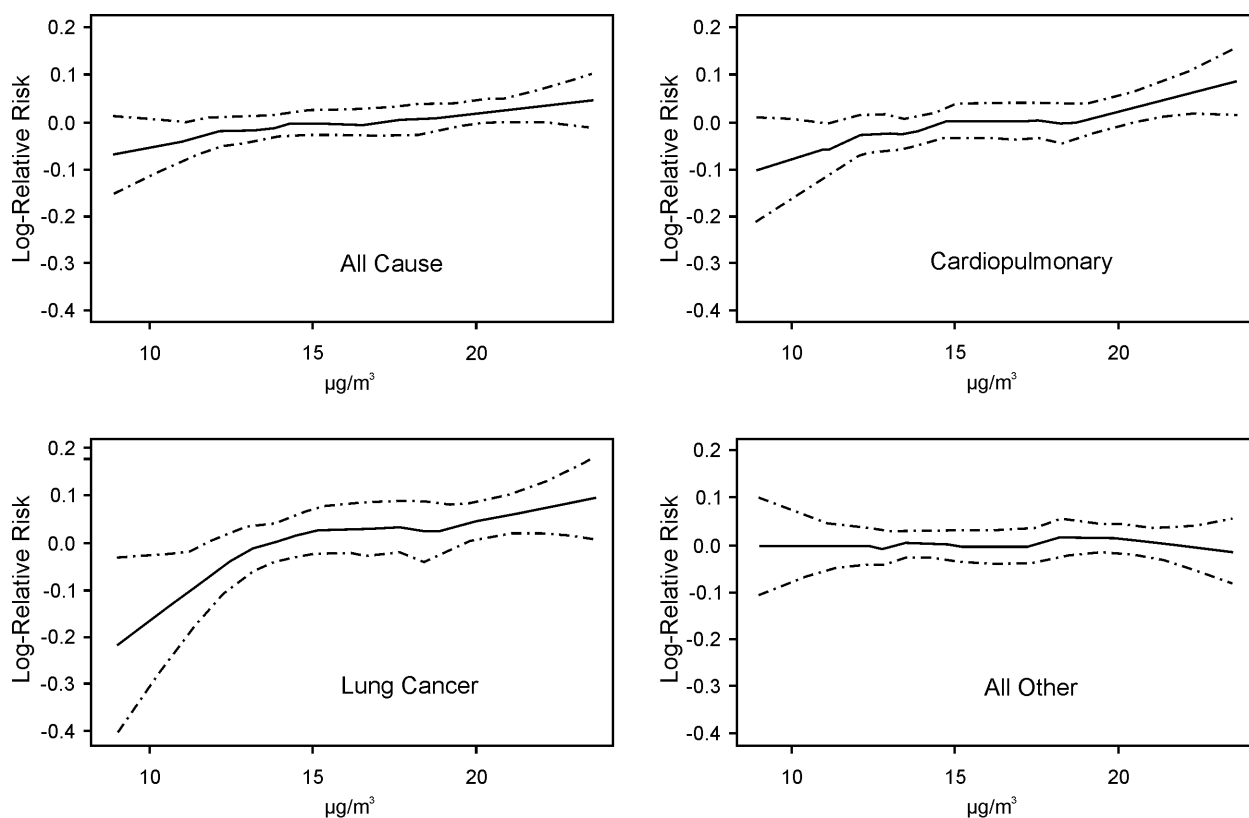
Figure 8-8. **Natural logarithm of relative risk for total and cause-specific mortality per 10 μg/m^3 PM$_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions. Based on (Pope et al., 2002) mean curve (solid line) with pointwise 95% confidence intervals (dashed lines).**

1   higher risk for total and lung cancer mortality than are women, slightly less for cardiopulmonary

2   mortality although still significant. Log(RR) decreases significantly from individuals with less

3   than a high school education to those with more than a high school education, replicating the

4   findings in Krewski et al. (2000), with twice the time on study. Including smoking status showed

5   increased fine particle RR for cardiopulmonary and lung cancer mortality in never-smokers and

6   least effect in current smokers, but for total mortality, significant or near-significant effects

7   occurred in both current and never-smokers, but not former smokers.

8   The second-stage random effects models on the right side of Figure 8-9 have much wider

9   confidence intervals than the first-stage models, but are still statistically significant for total,

10   cardiopulmonary, and lung cancer mortality. Spatial smoothing decreases the magnitude and

11   significance of the fine particle effect for total mortality. For cardiopulmonary mortality, spatial
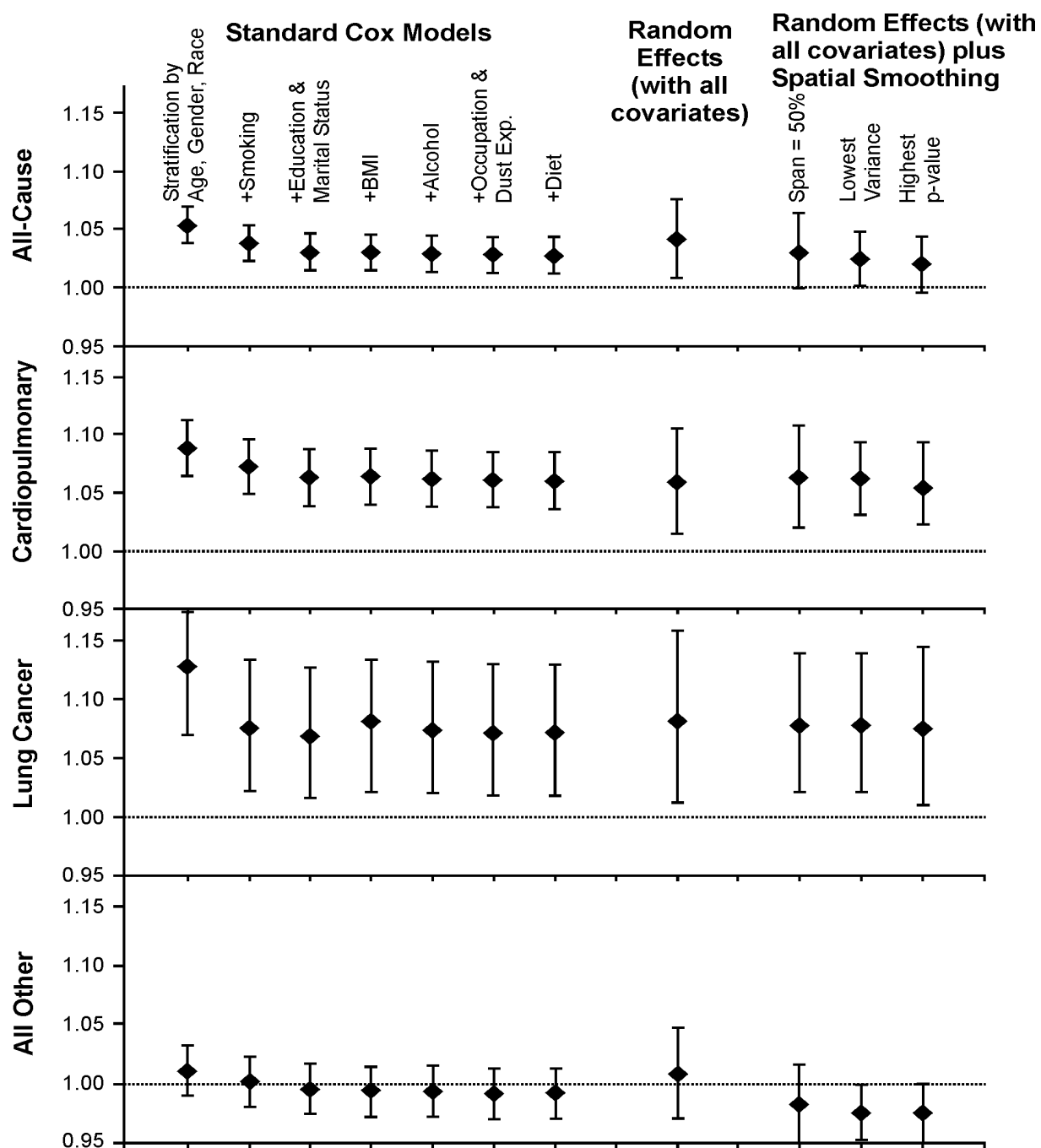
Figure 8-9. Relative risk of total and cause-specific mortality at 10 μg/m³ PM$_{2.5}$ (mean of 1979-1983) of alternative statistical models. The standard Cox models are built up in a sequential stepwise manner from the baseline model stratified by age, gender, and race by adding additional covariates. The random effects model allows for additional city-to-city variation, and the spatial smoothing models show the effects of increasingly aggressive adjustment for spatial correlation. Based on Pope et al. (2002).
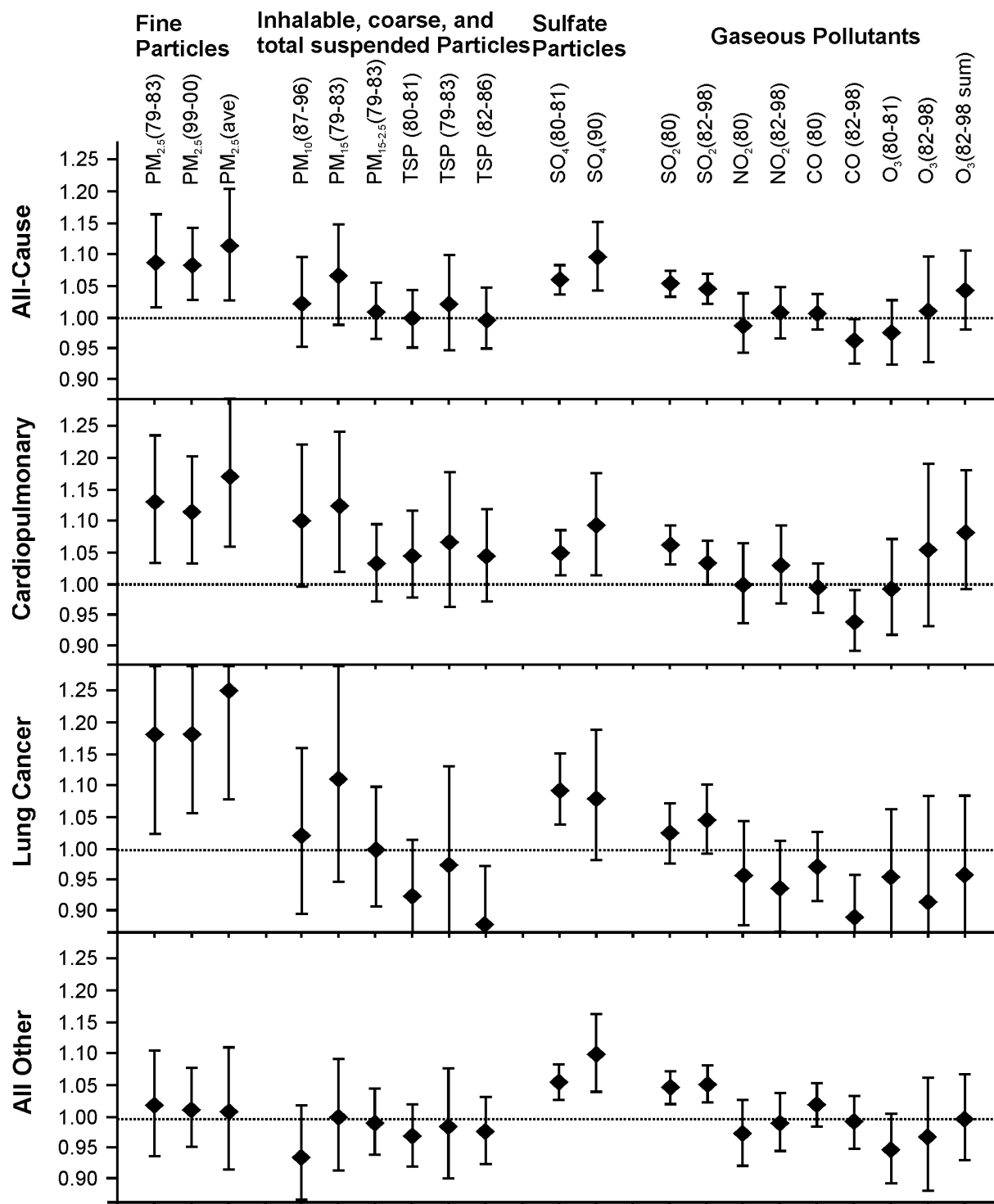
Figure 8-10. Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses). Based on Pope et al. (2002).

1   smoothing can increase the magnitude of the RR and increase its significance by reducing the

2   width of the confidence intervals in the "50%-span" and "lowest variance" smoothing methods.

3   For lung cancer mortality, spatial smoothing very slightly decreases the magnitude of the RR but

4   also increases its significance by reducing the width of the confidence intervals in the "50%-

5   span" and "lowest variance" smoothing methods.

6   Figure 8-10 shows a statistically significant relationship between fine particles and total,

7   cardiopulmonary, and lung cancer mortality whatever averaging span was used for $PM_{2.5}$, and

8   slightly larger for the average concentration of the 1979-1983 and 1999-2000 intervals. PM_{15} for

9   1979-1983 is significantly associated with cardiopulmonary mortality and marginally with total

10   mortality, whereas 1987-1996 PM_{15} is not quite significantly associated with cardiopulmonary

11   mortality only. Coarse particles and TSP are not significantly associated with any endpoint, but

12   are positively associated with cardiopulmonary mortality. Sulfate particles are very significantly

13   associated with all endpoints including mortality from all other causes, but only marginally for

14   lung cancer mortality using 1990 filters.

15   Figure 8-10 shows a highly significant relationship between SO_2 and all endpoints

16   including mortality from other causes, although weaker for lung cancer mortality. Ozone (using

17   only the third quarter for 1982-1998) shows a marginally significant relationship with

18   cardiopulmonary mortality, but not the year-round average. The other criteria pollutants, CO and

19   NO_2, are not significantly and positively related to any mortality endpoint, unlike the findings for

20   acute mortality studies.

21   This paper is noteworthy because it shows that the general pattern of findings in the first

22   eight years of the study (Pope et al., 1995; Krewski et al., 2000) could be reasonably extrapolated

23   to the patterns that remain present with twice the length of time on study and three times the

24   number of deaths. As shown later in Table 8-12 (Pg. 8-94), the excess relative risk estimate

25   (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for total mortality in the original ACS study (Pope et al., 1995) was

26   6.6% (3.6, 9.9%); in the ACS reanalysis (Krewski et al., 2000, Table 20, Full Model) it was 6.6%

27   (3.6, 9.9%); and, in the extended ACS data set (Pope et al., 2002), it was 4.1% (0.8, 7.5%) using

28   the 1979-1983 data and 6.2% (1.6, 11%) using the average of the 1979-1983 and 1999-2000 data.

29   The excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for cardiopulmonary mortality in

30   the original ACS study (Pope et al., 1995) was 11.6% (6.6, 16.7%); in the ACS reanalysis

31   (Krewski et al., 2000, Table 20, Full Model), it was 10.6% (5.9, 15.4%); and, in the extended

1   ACS data set (Pope et al., 2002), it was 5.9% (1.5, 10.5%) using the 1979-1983 data and 9.3%

2   (3.3, 15.8%) using the average of the 1979-1983 and 1999-2000 data. Thus, the additional data

3   and statistical analyses in (Pope et al., 2000) yield somewhat smaller estimates than in the

4   original study (Pope et al., 1995), but similar estimates to the reanalysis of the original ACS data

5   set (Krewski et al., 2000).

6   The authors draw the following conclusions:

7   (1) The apparent association between fine particle pollution and mortality persists with longer

8   follow-up as the participants in the cohort grow older and more of them die.

9   (2) The estimated fine particle effect on cardiopulmonary mortality and cancer mortality was

10   relatively stable, even after adjustment for smoking status, although the estimated effect was

11   larger and more significant for never-smokers vs. former or current smokers. The estimates

12   were relatively robust against inclusion of many additional covariates: education, marital

13   status, BMI, alcohol consumption, occupational exposure, and dietary factors. However, as

14   the authors note, the data on individual risk factors was collected only at the time of

15   enrollment and has not been updated, so that changes in these factors since 1982 could

16   introduce risk factor exposure mis-classification, with a loss of precision in the estimates

17   and might limit the ability to characterize time dependency of effects.

18   (3) Additional assessments for potential spatial or regional differences not controlled in the

19   first-stage model were evaluated. If there are unmeasured or inadequately modeled risk

20   factors that are different across locations or spatially clustered, then PM risk estimates may

21   be biased. If the clustering is independent or random or independent across areas, then

22   adding a random-effects component to the Cox proportional hazards model can deal with the

23   problem. However, if location is associated with air pollution, then the spatial correlation

24   may be evaluated using non-parametric smoothing methods. No significant spatial auto-

25   correlation was found after controlling for fine particles. Even after adjusting for spatial

26   correlation, the estimated $PM_{2.5}$ effects were significant and persisted for cardiopulmonary

27   mortality and lung cancer mortality and were borderline significant for total mortality, but

28   with much wider confidence intervals after spatial smoothing.

29   (4) Elevated total, cardiopulmonary, and lung cancer mortality risks were associated with fine

30   particles, but other mortality was not. PM_{10} for 1987-1996 and PM_{15} for 1979-1983 were

31   just significantly associated with cardiopulmonary mortality only, but $PM_{10-2.5}$ and TSP were

1   not associated with total or any cause-specific mortality. All endpoints were very

2   significantly associated with sulfates, except lung cancer with 1990 sulfate data. All

3   endpoints were very significantly associated with SO_2 using 1980 data, with total and other

4   mortality using the 1982-1998 data, but cardiopulmonary and lung cancer mortality had only

5   a borderline significant association with the 1982-1998 SO_2 data. None of the other gaseous

6   pollutants had a significant positive association with any endpoint, except for a borderline

7   association of third-quarter ozone to cardiopulmonary mortality. In summary, neither coarse

8   thoracic particles nor TSP were significantly associated with mortality, nor were NO2 and

9   CO on a long-term exposure basis. (It should be noted, however, that additional analyses

10   may yet be useful. The data would allow segmentation of mortality into smaller periods

11   rather than the whole 16 year duration of the mortality follow up, for example from 1982

12   through 1989 and from 1990 through 1998. In this way, it may be possible to evaluate any

13   changes in PM mortality rate over time.)

14   (5) The concentration-response curves estimated using non-parametric smoothers were all

15   monotonic and (except for lung cancer) nearly linear. However, the shape of the curve may

16   become non-linear at much higher concentrations.

17   (6) The excess risk from $PM_{2.5}$ exposure is much smaller than that estimated for cigarette

18   smoking for current smokers in the same cohort (Pope et al., 1995), RR = 2.07 for total

19   mortality, RR = 2.28 for cardiopulmonary mortality, and RR = 9.73 for lung cancer

20   mortality. In the more polluted areas of the United States, the relative risk for substantial

21   obesity (a known risk factor for cardiopulmonary mortality) is larger than that for $PM_{2.5}$, but

22   the relative risk from being moderately overweight is somewhat smaller.

23

24   ### 8.2.3.2.3 AHSMOG Analyses

25   The Adventist Health Study of Smog (AHSMOG) represents a third major U.S. prospective

26   cohort study of chronic PM exposure-mortality effects. In 1977, the study enrolled 6,338

27   non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to

28   95 years. The participants had resided for at least 10 years within 5 miles (8 km) of their then-

29   current residence locations, either within the three major California air basins (San Diego,

30   Los Angeles, or San Francisco) or else were part of a random 10% sample of Adventist Health

31   Study participants residing elsewhere in California. The study has been extensively described

1   and initial results reported elsewhere (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al.,

2   1991). In the latest AHSMOG analyses (Abbey et al., 1999), mortality status of the subjects after

3   ca. 15-years of follow-up (1977-1992) was determined by various tracing methods, finding 1,628

4   deaths (989 female, 639 male) in the cohort. This is a 50% percent increase in the follow-up

5   period vs. previous AHSMOG reports, which increases the power of the latest analyses over past

6   published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029 were

7   cardiopulmonary, 135 were non-malignant respiratory (ICD9 codes 460-529), and 30 were lung

8   cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category,

9   contributing respiratory causes (CRC). CRC included any mention of nonmalignant respiratory

10   disease as either an underlying or a "contributing cause" on the death certificate. Numerous

11   analyses were done for the CRC category, due to the large numbers and relative specificity of

12   respiratory causes as a factor in the deaths. Education was used to index socio-economic status,

13   rather than income. Physical activity and occupational exposure to dust were also used as

14   covariates.

15   Cox proportional hazard models adjusted for a variety of covariates, or stratified by sex,

16   were used. The "time" variable used in most of the models was survival time from date of

17   enrollment, except that age on study was used for lung cancer effects due to the expected lack of

18   short-term effects. A large number of covariate adjustments were evaluated, yielding results for

19   all non-external mortality as shown in Table 8-8 and described by Abbey et al. (1999).

20   Essentially no statistically significant PM related effects were observed for either males or

21   females, except RR = 1.08 for males in relation to 30 days per year with $PM_{10} > 100 \ \mu g/m^3$.

22   An analogous pattern of results was found for cause-specific mortality analyses of the

23   AHSMOG data. That is, positive and statistically significant effects on cardiopulmonary deaths

24   were found in models that included both sexes and adjustment for age, pack-years of smoking,

25   and body-mass index (BMI) (RR = 1.14, 95% CI 1.03-1.56 for 30 day/yr > 100 $\mu g/m^3$ PM_{10}).

26   Subsets of the cohort had elevated risks: (a) former smokers had higher RR's than never-

27   smokers (RR for PM_{10} exceedances for never-smokers was marginally significant by itself);

28   (b) subjects with low intake of anti-oxidant vitamins A, C, E had significantly elevated risk of

29   response to PM_{10}, whereas those with adequate intake did not (suggesting that dietary factors or,

30   possibly, other socio-economic or life style factors for which they are a surrogate may be

31   important covariates); and (c) there also appeared to be a gradient of PM_{10} risk with respect to

**TABLE 8-8. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL
CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE
COVARIATE MODEL IN THE ASHMOG STUDY**

Pollution Index	Pollution Incr.	Females			Males		
		RR	LCL	UCL	RR	LCL	UCL
$PM_{10}>100$, d/yr.	30 days/yr.	0.958	0.899	1.021	1.082	1.008	1.162
PM_{10} mean	20 $\mu g/m^3$	0.950	0.873	1.033	1.091	0.985	1.212
SO_4 mean	5 $\mu g/m^3$	0.901	0.785	1.034	1.086	0.918	2.284
$O_3>100$ ppb, h/yr.	551 h/yr. (IQR)	0.90	0.80	1.02	1.140	0.98	1.32
SO_2 mean	3.72 (IQR)	1.00	0.91	1.10	1.05	0.94	1.18

LCL = Lower 95% confidence limit   UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

1   time spent outdoors, with those who had spent at least 16 h/wk outside at greater risk from PM_{10}

2   exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a

3   modifying factor reflecting temporal variation in exposure to ambient air pollution is not certain.

4   For example, if the males spent much more time outdoors than females, outdoor exposure time

5   could be confounded with gender. When the cardiopulmonary analyses are broken down by

6   gender (Table 8-9), the RR's for female deaths were generally smaller than that for males,

7   although none of the risks for PM indices or gaseous pollutants were statistically significant.

8   The AHSMOG cancer analyses showed a confusing array of results for lung cancer mortality

9   (Table 8-10). For example, RR's for lung cancer deaths were statistically significant for males

10   for PM_{10} and O_3 metrics, but not for females. In contrast, such cancer deaths were significant for

11   mean NO_2 only for females (but not for males), but lung cancer metrics for mean SO_2 were

12   significant for both males and females. This pattern is not readily interpretable, but is reasonably

13   attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males),

14   resulting in wide RR confidence intervals and very imprecise effects estimates.

15   The analyses reported by Abbey et al. (1999) attempted to separate PM_{10} effects from those

16   of other pollutants by use of two-pollutant models, but no quantitative findings from such models

17   were reported. Abbey et al. mentioned that the PM_{10} coefficient for CRC remained stable or

TABLE 8-9. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Incr.	Females			Males		
		RR	LCL	UCL	RR	LCL	UCL
PM_{10}>100, d/yr.	30 days/yr.	0.929	0.857	1.007	1.062	0.971	1.162
PM_{10} mean	20 $\mu g/m^3$	0.933	0.836	1.042	1.082	0.943	1.212
SO_4 mean	5 $\mu g/m^3$	0.950	0.793	1.138	1.006	0.926	1.086
O_3>100 ppb, h/yr.	551 h/yr. (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O_3 mean	10 ppb	0.975	0.865	1.099	1.066	0.920	1.236
SO_2 mean	3.72 (IQR)	1.02	0.90	1.15	1.01	0.86	1.18

LCL = Lower 95% confidence limit   UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

TABLE 8-10. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Incr.	Smoking Category	Females			Males		
			RR	LCL	UCL	RR	LCL	UCL
PM_{10}>100, d/yr.	30 days/yr.	All[1]	1.055	0.657	1.695	1.831	1.281	2.617
PM_{10} mean	20 $\mu g/m^3$	All	1.267	0.652	2.463	2.736	1.455	5.147
NO_2 mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
O_3>100 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.50	12.07
O_3 mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO_2 mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.20
		never smokers	2.99	1.66	5.40			

[1]All = both never smokers and past smokers.
LCL = Lower 95% confidence limit   UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

1   increased when other pollutants were added to the model. Lung cancer mortality models for

2   males evaluated co-pollutant effects in detail and indicated that NO_2 was non-significant in all

3   two-pollutant models but the other pollutant coefficients were stable. The PM_{10} and O_3 effects

4   remained stable when SO_2 was added, suggesting possible independent effects, but PM_{10} and O_3

5   effects were hard to separate because these pollutants were highly correlated in this study.

6   Again, however, the very small number of lung cancer observations and likely great imprecision

7   of reported effects estimates markedly diminish the credibility of these results.

8   Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey

9   et al. (1999), but focused on lung cancer incidence (1977-1992). There were only 20 female and

10   16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be

11   specifically relevant to cancer, being the annual average of monthly exposure indices from

12   January, 1973 through the following months, but ending 3 years before date of diagnosis of the

13   case (i.e., representing a 3-year lag between exposure and diagnosis of lung cancer). The

14   covariates in the Cox proportional hazards model were pack-years of smoking and education, and

15   the time variable was attained age. Many additional covariates were evaluated for inclusion, but

16   only 'current use of alcohol' met criteria for inclusion in the final model. Pollutants evaluated

17   were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant,

18   including outdoor exposure times. The RR estimates for male lung cancer cases were:

19   (a) positive and statistically significant for all PM_{10} indicators; (b) positive and predominantly

20   significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in

21   former smokers; (c) positive and significant for mean SO_2, except when restricted to proximate

22   monitors; and (d) positive but not significant for mean NO_2. When analyses are restricted to use

23   of air quality data within 32 km of the residences of subjects, the RR over the IQR of 24 $\mu g/m^3$ in

24   the full data set is 5.21 (or RR=1.989 for 10 $\mu g/m^3$). The female RR's were all much smaller

25   than for males, not being statistically significant for any indicator of PM_{10} or O_3, but being

26   significant for mean SO_2.

27   The AHSMOG investigators also attempted to compare effects of fine vs. coarse particles

28   (McDonnell et al, 2000). For AHSMOG participants living near an airport (n=3,769), daily

29    $PM_{2.5}$ concentrations were estimated from airport visibility using previously-described methods

30   (Abbey et al, 1995b). Table 8-11 shows the results of this analysis for the male subset near

31   airports (n=1266). Given the smaller numbers of subjects in these subset analyses, it is not

TABLE 8-11. COMPARISON OF EXCESS RELATIVE RISKS FOR THREE PARTICLE METRICS IN THE MALE SUBSET OF THE AHSMOG STUDY

Underlying Cause of Mortality	PM Metric		
	$PM_{2.5}$	$PM_{10-2.5}$	PM_{10}
All causes	8.4.% (−2.1, 21%)	—	
	—	5.2% (−8.2, 21%)	9.9% (−4.1, 26%)
	9.3% (−3.8, 24%)	−1.0% (−16, 17%)	
Any contributing nonmalignant respiratory cause	22.6% (−2.9, 55%)	—	
	—	19.6% (−12, 64%)	30.5% (−4.8, 140%)
	19.8% (−8.8, 58%)	6.2% (−27, 54%)	
Lung cancer	39.1% (−21, 146%)	—	
	—	25.9% (−38, 156%)	51.2% (−30, 224%)
	35.7% (−28, 157%)	7.2% (−52, 137%)	

1   necessarily surprising that no pollutants are statistically significant in these regressions. It is

2   important, however, to caveat that the $PM_{2.5}$ exposures were estimated from visibility

3   measurements (increasing exposure measurement error), and a very uneven and clustered

4   distribution of exposures was presented by the authors. Also, the $PM_{10-2.5}$ values were calculated

5   from the differencing of PM_{10} and $PM_{2.5}$, likely contributing to additional measurement error for

6   the coarse particle ($PM_{10-2.5}$) variable used in the analyses.

7

8   *8.2.3.2.4 The EPRI-Washington University Veterans' Cohort Mortality Study*

9   Lipfert et al. (2000b) reported preliminary results from new large-scale mortality analyses

10   using a prospective cohort of up to 70,000 men assembled by the U.S. Veterans Administration

11   (VA) in the mid 1970s. While much smaller than the ACS cohort, this study group shares the

12   similarity that it was not originally formed to study air pollution, but was later linked to air

13   pollution data collected separately, much of it subsequent to the start of the study. The AHSMOG

14   and Six City studies were designed as prospective studies to evaluate long-term effects of air

15   pollution and had concurrent air pollution measurements. The ACS study was also a prospective

16   study, with air pollution data at about the approximate time of enrollment but not subsequently

1   (Pope et al., 1995). The extended ACS data incorporated much more air pollution data,

2   including TSP data back to the 1960s and more recent fine particle data. The $PM_{2.5}$ data set was

3   smaller than the TSP data set and similar to the ACS data.

4   The study cohort was male, middle-aged (51 ± 12 years) and included a larger proportion of

5   African-Americans (35%) than the U.S. population as a whole and a large percentage of current

6   or former smokers (81%). The cohort was selected at the time of recruitment as being mildly to

7   moderately hypertensive, with screening diastolic blood pressure (DBP) in the range 90 to

8   114 mm Hg (mean 96, about 7 mm more than the U.S. population average) and average systolic

9   blood pressure (SBP) of 148 mm Hg. The subjects had all been healthy enough to be in the U.S.

10   armed forces at one time. A comparison of their pre-existing health status at time of study

11   recruitment vs. the initial health status of the other cohorts would be of interest. The study that

12   led to the development of this clinical cohort (Veterans Administration Cooperative Study Group

13   on Antihypertensive Agents, 1970; 1967) was a "landmark" VA cooperative study demonstrating

14   that anti-hypertensive treatment markedly decreased morbidity and mortality (Perry et al., 1982).

15   The clinical cohort itself involved actual clinical rather than research settings. Some differences

16   between the VA cohort and other prospective cohorts are noted below.

17   Pollutant levels of the county of residence at the time of entry into the study were used for

18   analyses versus levels at the VA hospital area. Contextual socioeconomic variables were also

19   assembled at the ZIP-code and county levels. The ZIP-code level variables were average

20   education, income, and racial mix. County-level variables included altitude, average annual

21   heating-degree days, percentage Hispanic, and socioeconomic indices. Census tract variables

22   included poverty rate and racial mix. County-wide air pollution variables included TSP, PM_{10},

23   $PM_{2.5}$, PM_{15}, $PM_{15-2.5}$, SO_4, O_3, CO, and NO_2 levels at each of the 32 VA clinics where veterans

24   were enrolled. In addition to considering average exposures over the entire period, three

25   sequential mortality follow-up periods (1976-81, 1982-88, 1989-96) were also considered

26   separately in statistical analyses, which evaluated relationships of mortality in each of those

27   periods to air pollution in different preceding, concurrent, or subsequent periods (i.e., up to 1975,

28   1975-81, 1982-88, and 1989-86, for TSP in the first three periods, PM_{10} for the last, and NO_2,

29   95 percentile O_3, and 95 percentile CO for all four periods). Mortality in the above-noted periods

30   was also evaluated in relation to SO_4 in each of the same four periods noted for NO_2, O_3, and CO,

31   and to $PM_{2.5}$, PM_{15}, and $PM_{15-2.5}$ in 1979-81 and 1982-84.

1   The use of diastolic and systolic blood pressure in the reported regression results may

2   require further evaluation. The VA Cohort participants were recruited on the basis of initial

3   diastolic blood pressure (DBP) of 90 to 114 mm Hg.

4   The participants in the VA Cohort clearly formed an "at-risk" population, and the results by

5   Vasan et al. (2001) make more plausible the hypothesis in (Lipfert et al., 2000b, p. 62) that

6   ". . .the relatively high fraction of mortality within this cohort may have depleted it of susceptible

7   individuals in the later periods of follow-up." The role of DBP and SBP as predictors in

8   regression models in the VA Cohort may be considered as closer to the endpoint (mortality) than

9   as a more distal behavioral, environmental, or contextual predictor of mortality such as air

10   pollution, temperature, smoking behavior, BMI, etc. The author (F. Lipfert, personal

11   communication, March 28, 2002) notes that personal-level variables tend to interact only with

12   each other, as do county-level variables with little correlation across spatial scales.

13   The estimated mean risk of cigarette smoking in this cohort (1.43 Relative Risk) is also

14   smaller than that of the Six City cohort (RR = 1.59) and the ACS cohort (RR = 2.07 for a current

15   smoker). Some possible differences include the higher proportion of former or current smokers

16   in this cohort (81%) vs. 51% in the ACS study and 42 to 53% in the Six City study. A possibly

17   more important factor may be the difference in education levels, with only 12% of the ACS

18   participants having less than a high school education vs 28% of the Six City cohort and not

19   reported for the VA Cohort (although the Armed Services do have enlistment standards). The

20   education differences may be associated with smoking behavior. Also, the large number of

21   interaction terms in the model may account for part of the difference.

22   The preliminary screening models used proportional hazards regression models (Miller

23   et al., 1994) to identify age, SBP, DBP, body mass index (BMI, nonlinear), age and race

24   interaction terms, and present or former smoking as baseline predictors, with one or two

25   pollution variables added. In the final model using 233 terms (of which 162 were interactions of

26   categorized SBP, DBP, and BMI variables with age), the most significant non-pollution variables

27   were SBP, DBP, BMI, and their interactions with age, smoking status, average ZIP education,

28   race, poverty, height, and a clinic-specific effect. Lipfert et al. (2000b) noted that the risk of

29   current cigarette smoking (1.43) that they found was lower than reported in other studies. The

30   most consistently positive effects were found for O_3 and NO_2 exposures in the immediately

31   preceding years. This study used peak O_3 rather than mean O_3 as in some other cohort studies.

1   This may account for the higher O_3 and NO_2 effects here. While the PM analyses considering

2   segmented (shorter) time periods gave differing results (including significantly negative mortality

3   coefficients for some PM metrics), when methods consistent with the past studies were used (i.e.,

4   many year average PM concentrations), similar results were reported, with the authors finding

5   that "(t)he single-mortality-period responses without ecological variables are qualitatively similar

6   to what has been reported before ($SO_4 => PM_{2.5} > PM_{15}$)". With ecological variables included,

7   the only significant PM effect was that of TSP up to 1981 on 1976-81 mortality. It might be

8   instructive to evaluate more parsimonious regression models with fewer ecological covariates

9   and interaction terms. It is noteworthy that estimated PM effects appear to be smaller in the later

10 years of the study rather than in the earlier years. This may also be due to cohort depletion.

11

12 *8.2.3.2.5 Relationship of AHSMOG, Six Cities, ACS and VA Study Findings*

13   The results of the more recent AHSMOG mortality analyses (Abbey et al., 1999; McDonnell

14 et al., 2000) are compared here with findings from the earlier Six Cities study (Dockery et al.,

15 1993), the ACS study (Pope et al., 1995), the HEI reanalyses of the latter two studies, the

16 extension of the ACS study (Pope et al., 2002), and the VA study (Lipfert et al., 2000).

17 Table 8-12 compares the estimated RR for total, cardiopulmonary, and cancer mortality among

18 the studies. The number of subjects in these studies varies greatly (8,111 subjects in the

19 Six-Cities Study; 295,223 subjects in the 50 fine particle ($PM_{2.5}$) cities and 552,138 subjects in

20 the 151 sulfate cities of the ACS Study; 6,338 in the AHSMOG Study; 70,000 in the VA study);

21 and this may partially account for differences among their results.

22   As shown in Table 8-12, the Six Cities study found significant associations with all PM

23 indicators. In the Krewski et al. (2000) reanalysis of the ACS study data, larger associations

24 were found for both $PM_{2.5}$ and PM_{15} (excess relative risks of 6.6% for 10 $\mu g/m^3$ $PM_{2.5}$ and 4% for

25 20 $\mu g/m^3$ increments in annual PM_{15}, respectively), although both associations were significant.

26 Most recently, McDonnell et al. (2000) reported evidence from the AHSMOG analyses

27 suggestive of somewhat stronger associations with fine particles than coarse particles, though the

28 associations were only reported for males and none reached statistical significance.

29   Overall, the results most recently reported for the AHSMOG study (Abbey et al., 1999;

30 McDonnell et al., 2000) do not find consistent, statistically significant associations between

31 mortality and long-term PM exposure, though the authors conclude that some evidence was

TABLE 8-12. COMPARISON OF EXCESS RELATIVE RISKS OF LONG-TERM MORTALITY IN THE HARVARD SIX CITIES, ACS, AHSMOG, AND VA STUDIES

Study	PM[1]	Total Mortality		Cardiopulmonary Mortality		Lung Cancer Mortality	
		Ex. RR[2]	95% CI	Ex. RR	95% CI	Ex. RR	95% CI
Six City[3]	$PM_{2.5}$	13%	(4.2, 23%)	18%	(5.8, 32%)	18%	(−11, 57%)
Six City New[4]	$PM_{2.5}$	14%	(5.3, 23%)	19%	(6.3, 33%)	21%	(−8.4, 60%)
ACS[5]	$PM_{2.5}$	6.6%	(3.6, 9.9%)	11.6%	(6.6, 17%)	1.2%	(−8,7, 12%)
ACS[6] New	$PM_{2.5}$	7.0%	(4.0, 10%)	12.0%	(7.4, 17%)	0.8%	(−8.7, 11%)
ACS New	$PM_{15-2.5}$	0.3%	(−0.9, 1.8%)	0.3%	(−1.5%, 2.4%)	−0.9%	(−5.5%, 3.8%)
ACS New	$PM_{10/15}$ Dichot	4%	(1.0, 9%)	7%	(3, 12%)	0.4%	(−4.0, 5%)
ACS New	$PM_{10/15}$ SSI	2%	(−1.0, 4%)	6%	(3, 9%)	−0.8%	(−4.4, 3%)
ACS Extend.[7]	$PM_{2.5}$ 1979-83	4.1%	(0.8, 7.5%)	5.9%	(1.5, 10%	8.2%	(1.1, 16%)
ACS Extend.	$PM_{2.5}$ 1999-000	5.9%	(2.0, 9.9%)	7.9%	(2.3, 14%)	12.7%	(4.1, 22%)
ACS Extend.	$PM_{2.5}$ Avg.	6.2%	(1.6, 11%)	9.3%	(3.3, 16%)	13.5%	(4.4, 23%)
AHSMOG[8]	$PM_{10/15}$	2%	(−5, 9%)	1%	(−8, 10%)	174%[9]	(45, 415%)
AHSMOG[9]	30+ days $PM_{10/15}$ > 100	NA	NA	14%	(3, 26%)	NA	NA
AHSMOG[10]	$PM_{2.5}$	9.3%[11]	(−3.8, 24%)	20%[9]	(−9, 55%)	36%	(−28, 157%)
VA[12]	$PM_{2.5}$	-10.0%	(−15,−4.6%)				

[1]Increments are 10 $\mu g/m^3$ for $PM_{2.5}$ and 20 $\mu g/m^3$ for $PM_{10/15}$.

[2]Ex.RR (excess relative risk, percent) = 100 * (RR - 1) where the RR has been converted from the highest-to-lowest range to the standard increment Δ (10 or 20) by the equation.

$$RR = \exp(\log(RR \text{ for range}) \times \Delta/\text{range}).$$

[3]From (Dockery et al., 1993; Krewski et al., 2000, Part II, Table 21a), original model.

[4]From (Krewski et al., 2000), Part II, Table 21c.

[5]From (Krewski et al., 2000), Part II, Table 25a.

[6]From (Krewski et al., 2000), Part II, Table 25c.

[7]From (Pope et al., 2002).

[8]From (Abbey et al., 1999), pooled estimate for males and females.

[9]For males only; no significant excess risk for females with contributing respiratory causes.

[10]From (McDonnell et al., 2000), using two-pollutant (fine and coarse particle) models.

[11]Males only.

[12]Males only, exposure period 1979-81, mortality 1982-88 from Table 7 (Lipfert et al., 2000b).

1   suggestive of associations with fine particles. Also, the VA study (Lipfert et al., 2000) found no

2   association with $PM_{2.5}$. Nevertheless, the lack of consistent findings in the AHSMOG study and

3   negative results of the VA study, do not cast doubt on the findings of the Six Cities and ACS

4   studies; both of the late studies had larger study populations, were based on measured PM data

5   (in contrast with AHSMOG PM estimates based on TSP or visibility measurements), and have

6   been validated through exhaustive reanalysis. When considering the results of these four studies,

7   including the reanalyses results for the Six Cities and ACS studies and the results of the ACS

8   study extension, it can be concluded that there is substantial evidence for a positive association

9   between long-term exposure to PM (especially fine particles) and mortality.

10   There is no obvious statistically significant relationship between PM effect sizes, gender,

11   and smoking status across these studies. The AHSMOG analyses show no significant

12   relationships between PM_{10} and total mortality or cardiovascular mortality for either sex, and

13   only for male lung cancer incidence and lung cancer deaths in a predominantly non-smoking

14   sample. The ACS results, in contrast, show similar and significant associations with total

15   mortality for both "never smokers" and "ever smokers", although the ACS cohort may include a

16   substantial number of long-term former smokers with much lower risk than current smokers.

17   The Six Cities study cohort shows the strongest evidence of a higher PM effect in current

18   smokers than in non-smokers, with female former smokers having a higher risk than male former

19   smokers. This study suggests that smoking status may be viewed as an "effect modifier" for

20   ambient PM, just as smoking may be a health effect modifier for ambient O_3 (Cassino et al.,

21   1999).

22   When the ACS study results are compared with the AHSMOG study results for $SO_4^=$

23   ($PM_{10-2.5}$ and PM_{10} were not considered in the ACS study, but were evaluated in ACS reanalyses

24   [Krewski et al., 2000; Pope et al, 2002]), the total mortality effect sizes per 15 $\mu g/m^3$ $SO_4^=$ for the

25   males in the AHSMOG population are seen to fall between the Six-Cities and the ACS effect

26   estimates for males: RR=1.28 for AHSMOG male participants; RR=1.61 for Six-Cities Study

27   male non-smokers; and RR=1.10 for never smoker males in the ACS study. The AHSMOG

28   study 95% confidence intervals encompass both of those other studies' sulfate RR's.

29

30

8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition

8.2.3.3.1 Six Cites, ACS, and AHSMOG Study Results

Ambient PM consists of a mixture that may vary in composition over time and from place to place. This should logically affect the relative toxicity of PM indexed by mass at different times or locations. Some semi-individual chronic exposure studies have investigated relative roles of various PM components in contributing to observed air pollution associations with mortality. However, only a limited number of the chronic exposure studies have included direct measurements of chemical-specific constituents of the PM mixes indexed by mass measurements used in their analyses.

As shown in Table 8-13, the Harvard Six-Cities study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and $SO_4^=$ RR associations (as indicated by their respective 95% CI's and t-statistics) were more consistent than those for the coarser mass components. However, the effects of sulfate and non-sulfate $PM_{2.5}$ are indicated to be quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities; so, the Six-Cities results were much less conclusive for the acidic component of PM than for the other PM metrics measured over many years during the study. The Six-Cities study also yielded total mortality RR estimates for the reported range across those cities of $PM_{2.5}$ and $SO_4^=$ levels that, although not statistically different, were roughly double the analogous RR's for the TSP-PM_{15} and $PM_{15-2.5}$ mass components.

Table 8-14 presents comparative $PM_{2.5}$ and $SO_4^=$ results from the ACS study, indicating that both had substantial, statistically significant effects on all-cause and cardiopulmonary mortality. On the other hand, the RR for lung cancer was notably larger (and substantially more significant) for $SO_4^=$ than $PM_{2.5}$ (not significant).

The most recent AHSMOG study analysis reported by Abbey et al. (1999) used PM_{10} as its PM mass index, finding some significant associations with total and by-cause mortality, even after controlling for potentially confounding factors (including other pollutants). This analysis also considered $SO_4^=$ as a PM index for all health outcomes studied except lung cancer, but $SO_4^=$ was not as strongly associated as PM_{10} with mortality and was not statistically significant for any mortality category.

**TABLE 8-13. COMPARISON OF ESTIMATED RELATIVE RISKS FOR
ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH
THE REPORTED INTER-CITY RANGE OF CONCENTRATIONS
OF VARIOUS PARTICULATE MATTER METRICS**

PM Species	Concentration Range ($\mu g/m^3$)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
$SO_4=$	8.5	1.29	(1.06-1.56)	3.67
$PM_{2.5} - SO_4=$	8.4	1.24	(1.16-1.32)	8.79
$PM_{2.5}$	18.6	1.27	(1.06-1.51)	3.73
$PM_{15-2.5}$	9.7	1.19	(0.91-1.55)	1.81
$TSP-PM_{15}$	27.5	1.12	(0.88-1.43)	1.31

Source: Dockery et al. (1993); U.S. Environmental Protection Agency (1996a).

**TABLE 8-14. COMPARISON OF REPORTED $SO_4^=$ AND $PM_{2.5}$ RELATIVE
RISKS FOR VARIOUS MORTALITY CAUSES IN THE AMERICAN
CANCER SOCIETY (ACS) STUDY**

Mortality Cause	$SO_4^=$ (Range = 19.9 $\mu g/m^3$)			$PM_{2.5}$ (Range = 24.5 $\mu g/m^3$)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

Also, very extensive results were reported in Lipfert et al. (2000b) for various components: TSP, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, PM_{15}, $SO_4^=$. There were no significant positive effects for any exposure period concurrent or preceding the mortality period for any PM component, but there was for O_3.

Results from the Harvard Six Cities, the ACS, and the AHSMOG studies are compared in Table 8-15 (for total mortality) and Table 8-16 (for cause-specific mortality). Results for the VA study are not shown in Tables 8-15 and 8-16 for two reasons. First of all, the cohort is male and

**TABLE 8-15. COMPARISON OF TOTAL MORTALITY RELATIVE RISK
ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS
IN THREE PROSPECTIVE COHORT STUDIES**

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 μg/m^3)	Six Cities	All	1.504[a]; 1.530[b]	**2.94[a]; 3.27[b]**
		Male Nonsmoker	1.280[a]	0.81[a]
	AHSMOG	Male Nonsmoker	1.242	1.616
$PM_{2.5}$ (25 μg/m^3)	Six Cities	All	1.364[a]; 1.379[b]	**2.94[a]; 3.73[b]**
		Male Nonsmoker	1.207[a]	0.81[a]
	ACS (50 cities)	All	1.174	**4.35**
		Male Nonsmoker	1.245	**1.96**
$SO_4=$ (15 μg/m^3)	Six Cities	All	1.504[a]; 1.567[b]	**2.94[a]; 3.67[b]**
		Male Nonsmoker	1.359	0.81[a]
	ACS (151 cities)	All	1.111	**5.107**
		Male Nonsmoker	1.104	1.586
	AHSMOG	Male Nonsmoker	1.279	0.960
Days/yr. with PM_{10}>100 μg/m^3 (30 days)	AHSMOG	Male Nonsmoker	1.082	**2.183**
$PM_{10-2.5}$ (25 μg/m^3)	Six Cities	All	1.814[a]; 1.560[b]	**2.94[a,c]** 1.816[b]
		Male Nonsmoker	1.434[a]	0.81[a]

[a]Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
[b]Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996a).
[c]Method 1 not recommended for $PM_{10-2.5}$ analysis, due to high concentration in Topeka.

1   largely current or former smokers (81%), thus not comparable to the total or male non-smoker

2   populations. Secondly, there is a wide variety of exposure periods and mortality periods.

3   Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the

4   most versus least polluted city in Table 3 of Dockery et al. (1993) adjusted to standard

5   increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection

6   Agency (1996a). The Six Cities study of eastern and mid-western U.S. cities suggests a strong

7   and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly

TABLE 8-16. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.744[a]	**2.94**[a]
	AHSMOG	Male Nonsmoker	1.219	1.120
		Male Non-CRC[c]	1.537	**2.369**
$PM_{2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.527[a]	**2.94**[a]
	ACS (50 cities)	All	1.317	**4.699**
		Male	1.245	**3.061**
		Male Nonsmoker	1.245	1.466
SO_4= (15 $\mu g/m^3$)	Six Cities	All	1.743[a]	**2.94**[a]
	ACS (151 cities)	All	1.190	**5.470**
		Male	1.147	**3.412**
		Male Nonsmoker	1.205	**2.233**
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non.-CRC[c]	1.219	0.357
Days/yr. with PM_{10}>100 (30 days)	AHSMOG	Male Nonsmoker	1.082	1.310
		Male Non.-CRC[c]	1.188	**2.370**
$PM_{10-2.5}$ (25 $\mu g/m^3$)	Six Cities	All	2.251[a]	**2.94**[a,b]

[a]Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
[b]Method 1 not recommended for $PM_{10-2.5}$ analysis due to high concentration in Topeka.
[c]Male non. - CRC = AHSMOG subjects who died of any contributing non-malignant respiratory cause.

1   significant relationship to PM_{10}, and a marginal relationship to $PM_{10-2.5}$. The ACS study looked at

2   a broader spatial representation of cities, and found a stronger statistically significant relationship

3   to $PM_{2.5}$ than to sulfate (no other pollutants were examined). The AHSMOG study at California

4   sites (where sulfate levels are typically low) found significant effects in males for PM_{10}

5   100 $\mu g/m^3$ exceedances and a marginal effect of mean PM_{10}, but no PM effects for females or

6   with sulfates. On balance, the overall results shown in Tables 8-15 and 8-16 suggest statistically

1   significant relationships between long-term exposures to PM_{10}, $PM_{2.5}$, and/or sulfates and excess

2   total and cause-specific cardiopulmonary mortality.

3   Overall, the semi-individual long-term PM exposure studies conducted to-date collectively

4   confirm earlier cross-sectional study indications that the fine mass component of PM_{10} (and

5   usually especially its sulfate constituent) are more strongly correlated with mortality than is the

6   coarse $PM_{10-2.5}$ component. However, the greater precision of $PM_{2.5}$ population exposure

7   measurement (both analytical and spatial) relative to $PM_{10-2.5}$ makes conclusions regarding their

8   relative contributions to observed PM_{10}-related associations less certain than if the effect of their

9   relative errors of measurement could be addressed.

10   Single-pollutant results about PM components are informative, as shown in Table 8-15 for

11   total mortality and in Table 8-16 for cardiopulmonary causes. The t-statistics are compared for

12   studies where appropriate: mean PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and sulfate for the Six Cities (Dockery

13   et al., 1993); mean $PM_{2.5}$ and sulfate for ACS (Pope et al., 1995); mean PM_{10} and sulfate, and

14   PM_{10} exceedances of 100 $\mu g/m^3$ for AHSMOG (Abbey et al., 1999).

15

16   *8.2.3.3.2 Lipfert and Morris (2002): An Ecological Study*

17   Although we have identified reasons for preferring to use prospective cohort studies to

18   assess the long-term exposure effects of particles and gases, additional useful information may

19   still be provided by ecological studies, particularly by repeated cross-sectional studies that may

20   provide another tool for examining changes in air-pollution-attributable mortality over time.

21   Lipfert and Morris (2002) carried out cross-sectional regressions for five time periods using

22   published data on mortality, air pollution, climate, and socio-demographic factors using county-

23   level data. Data were available for TSP and gaseous co-pollutants as far back as 1960 and for

24   $PM_{2.5}$, PM_{15}, and $SO_4^=$ from the IPN. Attributable mortality at ages 45+ for 1979-1981 was

25   associated with TSP 1960-64, less strongly with TSP 1970-1974, but not with concurrent (1979-

26   1981) TSP. Attributable mortality for ages 45+ in 1979-1981 was associated with $PM_{2.5}$ and

27   $SO_4^=$ but not PM_{15} for 1979-1984. However, $SO_4^=$ for most intervals 1960-64 up to 1979-1981

28   was associated with mortality for most ages . Concurrent SO_2 (1979-1981) was associated with

29   mortality, but much less for earlier years.

30   Pollution-attributable mortality in 1989-91 was no longer significantly associated with TSP,

31   but remained significantly associated with $PM_{2.5}$ and $SO_4^=$ for ages 45+ for most time intervals:

1   1979-84, 1999, for $PM_{2.5}$, and 1970-74, 1979-81, 1979-84 (fines), 1982-88 for $SO_4^=$. Pollution-

2   attributable mortality in 1995-1997 had little association with present or previous $PM_{2.5}$ and

3   PM_{10}, but a reasonably consistent and positive relationship to $SO_4^=$. There appeared to be a

4   systematic decrease in the TSP, IPN, $PM_{2.5}$, and PM_{10} effects from the 1960s to the 1990s, and in

5   the AIRS and IPN $SO_4^=$ effect over time, but an increase in the AIRS $PM_{2.5}$ effect and in the NO_2

6   and peak O_3 effects.

7   One of the journal editors (Ayres, 2002) notes that this study uses some other ecological

8   variables that may improve the model. Two of the ecological variables, (vehicle miles of travel

9   per square mile per year by gasoline (VMTG) and diesel (VMTD) vehicles respectively in a

10   county, also used in Janssen et al., 2002) are likely to have important associations with air

11   pollution. As noted earlier, some ambient pollutants associated with fuel combustion have

12   higher concentrations near main roads, such as $PM_{10-2.5}$ (EC if from diesel exhaust) , NO_2, and

13   CO, whereas other pollutants such as O_3 may have higher concentrations away from major

14   highways.

15

16   **8.2.3.4 Population-Based Mortality Studies in Children**

17   Older cross-sectional mortality studies suggest that the very young may represent an

18   especially susceptible sub-population for PM-related mortality. For example, Lave and Seskin

19   (1977) found mortality among those 0-14 years of age to be significantly associated with TSP.

20   More recently, Bobak and Leon (1992) studied neonatal (ages < 1 mo) and post-neonatal

21   mortality (ages 1-12 mo) in the Czech Republic and reported significant and robust associations

22   between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal

23   respiratory mortality showed highly significant associations for all pollutants considered, but only

24   PM_{10} remained significant in simultaneous regressions. The exposure duration was longer than a

25   few days, but shorter than in the adult prospective cohort studies. Thus, the limited available

26   studies reviewed in the 1996 PM AQCD were highly suggestive of an association between

27   ambient PM concentrations and infant mortality, especially among post-neonatal infants.

28   More recent studies since the 1996 PM AQCD have focused specifically on ambient PM

29   relationships to (a) intrauterine mortality and morbidity and (b) early post neonatal mortality. In

30   a study by Pereira et al. (1998), of intrauterine (pre-natal) mortality during one year (1991-1992)

31   in Brazil, PM_{10} was not found to be a significant predictor, but involvement of CO was suggested

1   by an association between increased carboxyhemoglobin (COHb) in fetal blood and ambient CO

2   levels on the day of delivery measured in a separate study. Another study (Dejmek et al., 1999)

3   evaluated possible impacts of ambient PM_{10} and $PM_{2.5}$ exposure (monitored by EPA-developed

4   VAPS methods) during pregnancy on intrauterine growth retardation (IUGR) risk in the highly

5   polluted Teplice District of Northern Bohemia in the Czech Republic during three years

6   (1993-1996). Mean levels of pollutants (PM, NO_2, SO_2) were calculated for each month of

7   gestation and three concentration intervals (low, medium, high) derived for each pollutant.

8   Preliminary analyses found significant associations of IUGR with SO_2 and PM_{10} early in

9   pregnancy but not with NO_2. Odds ratios for IUGR for PM_{10} and $PM_{2.5}$ levels were determined

10   by logistic regressions for each month during gestation, after adjusting for potential confounding

11   factors (e.g., smoking, alcohol consumption during pregnancy, etc.). Definition of an IUGR birth

12   was any one for which the birth weight fell below the 10th percentile by gender and age for live

13   births in the Czech Republic (1992-93). The OR's for IUGR were significantly related to PM_{10}

14   during the first month of gestation: that is, as compared to low PM_{10}, the medium level PM_{10}

15   OR = 1.47 (CI 0.99-2.16), and the high level PM_{10} OR = 1.85 (CI 1.29-2.66). $PM_{2.5}$ levels were

16   highly correlated with PM_{10} (r = 0.98) and manifested similar patterns (OR = 1.16, CI 0.08-0.69

17   for medium $PM_{2.5}$ level; OR = 1.68, CI 1.18-2.40 for high $PM_{2.5}$ level). These results suggest

18   effects of PM exposures (probably including fine particles such as sulfates, acid aerosols, and

19   PAHs in the Teplice ambient mix) early in pregnancy (circa embryo implantation) on fetal

20   growth and development.

21   A recent study relating air pollution to birth weight in the metropolitan Reno, Nevada area

22   (Chen et al., 2002) examined the associations between air pollutant variables and birth weight

23   (BW) as a continuous variable and the prevalence of low birth weight (LBW, BW < 2500 gtn) as

24   a dichotomous variable. Mean daily concentrations of the pollution variables PM_{10}, O_3, and CO

25   were relatively low: 31.5 $\mu g/m^3$ for PM_{10} (range 1 to 157), 27.2 ppb for O_3 (range 2.8 to 62), and

26   1.0 ppm for CO (range 0.25 to 4.9). Ordinary least squares regression of BW on one, two, or

27   three air pollutants, and numerous covariates (e.g., age, race, education, prenatal care, maternal

28   behaviors) were included in the models. Third-trimester maternal exposure to PM_{10} was

29   significantly associated with an approximately 1 g reduction in BW per $\mu g/m^3$ PM_{10}, a finding

30   robust across different model specifications. Another finding was that the reduction in BW was

31   9 to 12 g for third-trimester exposures > 90th percentile PM_{10} (45 $\mu g/m^3$). However, none of the

1 PM odds ratios were significantly associated with increased risk of LBW. Neither ambient CO

2 nor O_3 were associated were significantly associated with LBW, unlike findings for intrauterine

3 growth reduction (IUGR) in Los Angeles by Ritz and Yu (1999) and Ritz et al. (2002).

4   More consistent results indicating likely early post-natal PM exposure effects on neonatal

5 infant mortality have emerged from other new studies. Woodruff et al. (1997), for example, used

6 cross-sectional methods to evaluate possible association of post-neonatal mortality with ambient

7 PM_{10} pollution. This study involved an analysis of a cohort of circa 4 million infants born during

8 1989 - 1991 in 86 U.S. metropolitan statistical areas (MSAs). Data from the National Center for

9 Health Statistics-linked birth/infant death records were combined at the MSA level with PM_{10}

10 data from EPA's Aerometric database. Infants were categorized as having high, medium, or low

11 exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Relationships

12 between this early neonatal PM_{10} exposure and total and cause-specific post-neonatal mortality

13 rates (from 1 mo to 1 y of age) were examined using logistic regression analyses, adjusting for

14 demographic and environmental factors. Overall post-neonatal mortality rates per 1,000 live

15 births were 3.1 among infants in areas with low PM_{10} exposures, 3.5 among infants with medium

16 PM_{10} exposures, and 3.7 among highly PM exposed infants. After adjustment for covariates, the

17 odds ratio (OR) and 95% confidence intervals for total post-neonatal mortality for the high

18 versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high

19 PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85)

20 and sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies,

21 high PM_{10} exposure was positively (but not significantly) associated with mortality from

22 respiratory causes (OR = 1.18, CI=0.86-1.61). However, other pollutants (e.g., CO) were not

23 considered as possible confounders. This study provides results consistent with some earlier

24 reports indicating that outdoor PM air pollution may be associated with increased risk of post-

25 neonatal mortality (e.g., Bobak and Leon, 1992), but lack of consideration of other air pollutants

26 as potential confounders in this new study reduces the certainty that PM is the specific causal

27 outdoor air pollutant in this case.

28   Lipfert et al. (2000c) have reported replicating the basic findings of Woodruff et al. (1997)

29 using a similar modeling approach but annual average PM_{10} air quality data for one year (1990)

30 instead of PM_{10} averaged over the first two post natal months during 1989-1991. The

31 quantitative relationship between the individual risk of infant mortality did not differ among

1   infant categories (by age, by birthweight, or by cause), but PM_{10} risks for SIDs deaths were

2   higher for babies of smoking mothers. $SO_4^=$ was a strong negative predictor of SIDs mortality for

3   all age and birth weight categories. The authors (a) noted difficulties in ascribing the reported

4   PM_{10} and $SO_4^=$ associations to effects of the PM pollutants per se versus the results possibly

5   reflecting interrelationships between the air pollution indices, a strong well-established

6   East-West gradient in U.S. SIDS cases, and/or underlying sociodemographic factors (e.g., the

7   socioeconomic or education level of parents) and (b) hypothesized that a parallel gradient in use

8   of wood burning in fireplaces or woodstoves and consequent indoor wood smoke exposure might

9   explain the observed cross-sectional study results.

10   The basic findings from Woodruff et al. (1997) also appear to be bolstered by a more recent

11   follow-up study by Bobak and Leon (1999), who conducted a matched population-based

12   case-control study covering all births registered in the Czech Republic from 1989 to 1991 that

13   were linked to death records. They used conditional logistic regression to estimate the effects of

14   suspended particles and nitrogen oxides on risk of death in the neonatal and early post-neonatal

15   period, controlling for maternal socioeconomic status and birth weight, birth length, and

16   gestational age. The effects of all pollutants were strongest in the post-neonatal period and

17   specific for respiratory causes. Only PM showed a consistent association when all pollutants

18   were entered in one model. Thus, in this study, it appears that long-term exposure to PM is the

19   air pollutant metric most strongly associated with excess post-neonatal deaths.

20   A study of changes in annual air pollution and infant mortality over time (rather than

21   spatially) in the U.S. was also recently conducted for the period 1981-1982 (Chay and

22   Greenstone, 2001a,b). These studies used sharp, differential air quality changes across sites

23   attributable to geographic variation in the effects of the 1981-1982 recession to estimate the

24   relationship between PM air pollution and infant mortality. During the narrow period of these

25   two years, there was substantial variation across counties in changes in particulate (TSP)

26   pollution and these differential pollution reductions appeared to be independent of changes in

27   numerous socioeconomic and health care factors that may be related to infant mortality. The

28   authors found that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per

29   100,000 live births at the county level (a 0.35-0.45 elasticity), the estimates being remarkably

30   stable across a variety of specifications. The estimated effects in this study were driven almost

31   entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal),

1 suggesting that fetal exposure to pollution (via the mother) may have adverse health

2 consequences. Findings of the population reductions in infant birth weight in this study provide

3 evidence consistent with the infant mortality effects found, suggestive of a causal relationship

4 between PM exposure and infant mortality.

5   The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995

6 adds additional interesting information pointing towards likely fine particle impacts on infant

7 mortality. That is, in Mexico City (where mean 24-h $PM_{2.5} = 27.4$ $\mu g/m^3$), infant mortality was

8 found to be associated with $PM_{2.5}$, NO_2, and O_3 in single pollutant GAM Poisson models, but

9 much less consistently with NO_2 and O_3 than $PM_{2.5}$ in multipollutant models. The estimated

10 excess risk for $PM_{2.5}$-related infant mortality lagged 3-5 days was 18.2% (95% CI 6.4, 30.7) per

11 25 $\mu g/m^3$ $PM_{2.5}$. It is not clear, however, the extent to which such a notable increased risk for

12 infant mortality might be extrapolated to U.S. situations, due to possible differences in prenatal

13 maternal or early postnatal infant nutritional status.

14

15 **8.2.3.5   Salient Points Derived from Analyses of Chronic Particulate Matter Exposure**
16 **Mortality Effects**

17   A review of the studies summarized in the previous PM AQCD (U.S. Environmental

18 Protection Agency, 1996a) indicates that past epidemiologic studies of chronic PM exposures

19 collectively indicate increases in mortality to be associated with long-term exposure to airborne

20 particles of ambient origins. The PM effect size estimates for total mortality from these studies

21 also indicate that a substantial portion of these deaths reflected cumulative PM impacts above

22 and beyond those exerted by acute exposure events.

23   The recent HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski

24 et al., 2000) "replicated the original results, and tested those results against alternative risk

25 models and analytic approaches without substantively altering the original findings of an

26 association between indicators of particulate matter air pollution and mortality." Several

27 questions, including the questions (1-4) posed at the outset of this Section (8.2.3) were

28 investigated by the Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies

29 data sets. Key results emerging from the HEI reanalyses and other new chronic PM mortality

30 studies are as follow:

1   (1) A much larger number of confounding variables and effects modifiers were considered

2   in the Reanalysis Study than in the original Six City and ACS studies. The only significant air

3   pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2, which greatly decreased the $PM_{2.5}$

4   and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38).

5   A similar reduction in particle effects occurred in any multi-pollutant model with SO_2. The most

6   important new effects modifier was education. The AHSMOG study suggested that other metrics

7   for air pollution, and other personal covariates such as time spent outdoors and consumption of

8   anti- oxidant vitamins, might be useful. Both individual- level covariates and ecological-level

9   covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated.

10   (2) Specific attribution of excess long-term mortality to any specific particle component or

11   gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$ and sulfate were

12   significantly associated with excess total mortality and cardiopulmonary mortality and to about

13   the same extent whether the air pollution data were mean or median long-term concentrations or

14   whether based on Original Investigator or Reanalysis Team data. The association of mortality

15   with PM_{15} was much smaller, though still significant, and the associations with the coarse

16   fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was

17   significant only for sulfate with the original investigator data or for new investigators with

18   regional sulfate artifact adjustment for the 1980-1981 data (Krewski et al., 2000, Part II,

19   Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous

20   co-pollutants were generally non-significant except for SO_2 (Krewski et al., 2000, Part II, Tables

21   32, 34-38) which was highly significant, and for cardiopulmonary disease with warm-season

22   ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very high,

23   and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000,

24   p. 234) concluded that, "Collectively, our reanalyses suggest that mortality may be associated

25   with more than one component of the complex mix of ambient air pollutants in urban areas of the

26   United States." In the most recent extension of the ACS study, Pope et al. (2002) confirmed the

27   strong association with SO_2 but found little evidence of effects for long-term exposures to other

28   gaseous pollutants.

29   (3) The extensive temporal data on air pollution concentrations over time in the Six City

30   Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure

31   to a much greater extent than reported in Dockery et al. (1993). The first approach was to

1   estimate the log- hazard ratio as a function of follow up time using a flexible spline-function

2   model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4 and $PM_{2.5}$ suggest

3   very similar relationships, with larger risk after initial exposure decreasing to 0 after about 4 or

4   5 years, and a large increase in risk at about 10 years follow-up time.

5   The analyses of the ACS Study proceeded somewhat differently, with less temporal data

6   but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of

7   estimated cumulative exposure (not defined) were very nonlinear and showed quite different

8   relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the

9   mortality log-hazard ratio increasing up to about 15 μg/m^3 and relatively flat above about

10   22 μg/m^3, then increasing again. The sulfate relationship is almost piecewise linear, with a low

11   near- zero slope below about 11 μg/m^3 and a steep increase above that concentration.

12   A third approach evaluated several time-dependent $PM_{2.5}$ exposure indicators in the Six

13   City study. They are: (a) constant (at the mean) over the entire follow-up period; (b) annual

14   mean within each of the 13 years of the study; (c) city-specific mean concentration for the earliest

15   years of the study, i.e., very long-term effect; (d) exposure estimate in 2 years preceding death;

16   (e) exposure estimate in 3 to 5 years preceding death; (f) exposure estimate > 5 years preceding

17   death. The time-dependent estimates (a-e) for mortality risk are generally similar and statistically

18   significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per 24.5 μg/m^3 being

19   much lower than the risk of 1.31 estimated for exposure at the constant mean for the period.

20   Thus, it is highly likely the duration and time patterns of long-term exposure affect the risk of

21   mortality, and further study of this question (along with that of mortality displacement from

22   short-term exposures) would improve estimates of life-years lost from PM exposure.

23   (4) The Reanalysis Study also advanced our understanding of the shape of the relationship

24   between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II,

25   Figure 6) found a visually near-linear relationship between all-cause and cardiopulmonary

26   mortality residuals and mean sulfate concentrations, near-linear between cardiopulmonary

27   mortality and mean $PM_{2.5}$, but a somewhat nonlinear relationship between all-cause mortality

28   residuals and mean $PM_{2.5}$ concentrations that flattens above about 20 μg/m^3. The confidence

29   bands around the fitted curves are very wide, however, neither requiring a linear relationship nor

30   precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality

relationship for other indicators may be useful in identifying a threshold, if one exists, for chronic PM exposures.

(5) With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies have generally found the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality. While relative measurement errors of various PM indicators must be further evaluated as a possible source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective semi-individual studies both indicate that the fine mass components of PM are more strongly associated with mortality effects of chronic PM exposure than are coarse fraction indicators.

8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE

This morbidity discussion is presented below in several subsections, dealing with: (a) acute cardiovascular morbidity effects of ambient PM exposure; (b) effects of short-term PM exposure on the incidence of respiratory and other medical visits and hospital admissions; and (c) short- and long-term PM exposure effects on lung function and respiratory symptoms in asthmatics and non-asthmatics.

8.3.1 Cardiovascular Effects Associated with Acute Ambient Particulate Matter Exposure

8.3.1.1 Introduction

Very little information specifically addressing acute cardiovascular morbidity effects of PM existed at the time of the 1996 PM AQCD. Since that time, a significantly expanded body of literature has emerged, both on the ecologic relationship between ambient particles and cardiovascular hospital admissions and on physiological and/or biochemical measures that have been associated with PM exposures. The latter studies are particularly important in that they suggest possible mechanisms.

This section begins with a brief summary of the conclusions that were reached in the 1996 PM AQCD regarding acute cardiovascular impacts of PM. Next, new studies are reviewed in the two categories noted above, i.e., ecologic time series studies and individual-level studies of physiological measures of cardiac function and/or biochemical measures in blood as they relate

1   to ambient pollution. This review is followed by discussion of several issues that are important

2   in interpreting the available data, including the identification of potentially susceptible sub-

3   populations, the roles of environmental co-factors such as weather and other air pollutants,

4   temporal lags in the relationship between exposure and outcome, and the relative importance of

5   various size-classified PM components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$).

6   Studies of cardiovascular PM effects presented in this section were identified by ongoing

7   Medline searches in conjunction with other search strategies. Specific studies were summarized

8   in text and/or tables based on criteria that include the following: (1) preference was given to

9   results reported for PM_{10}, $PM_{10-2.5}$, and $PM_{2.5}$; (2) studies relating cardiovascular effects to levels

10   of ambient PM exposure in a quantitative manner are the focus of presentations; and (3) other

11   factors discussed earlier in Section 8.1 of this chapter.

12

13   **8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate**
14   **   Matter Air quality Criteria Document**

15   Just two studies were available for review in the 1996 PM AQCD that provided data on

16   acute cardiovascular morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995).

17   Both studies were of ecologic time series design, using standard statistical methods. Analyzing

18   four years of data on the $\geq$ 65 year old Medicare population in Detroit, MI, Schwartz and Morris

19   (1995) reported significant associations between ischemic heart disease admissions and PM_{10},

20   controlling for environmental covariates. Based on an analysis of admissions data from

21   168 hospitals throughout Ontario, Canada, Burnett and colleagues (1995) reported significant

22   associations between fine particle sulfate concentrations, as well as other air pollutants, and daily

23   cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for

24   respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the

25   basis of these studies that: "There is a suggestion of a relationship to heart disease, but the

26   results are based on only two studies, and the estimated effects are smaller than those for other

27   endpoints" (U.S. Environmental Protection Agency, 1996a p. 12-100). The PM AQCD went on

28   to state that acute impacts on CVD admissions had been demonstrated for elderly populations

29   (i.e., $\geq$ 65), but that insufficient data existed to assess relative impacts on younger populations.

30   When viewed alongside the more extensive literature on acute CVD mortality that was

31   available at that time, the evidence from ecologic time series studies reviewed in the 1996 PM

1   AQCD was consistent with the notion that acute health risks of PM are larger for cardiovascular

2   and respiratory causes than for other causes. Given the tendency for end-stage disease states to

3   include both respiratory and cardiovascular impairment, and the associated diagnostic overlap

4   that often exists, it was not possible on the basis of these studies alone to determine which of the

5   two organ systems, if either, was more critically impacted.

6

7   **8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies**

8   *8.3.1.3.1 Acute Hospital Admission Studies in United States Cities*

9   Numerous new studies have examined associations between daily measures of ambient PM

10   and daily hospital admissions for cardiovascular disease (see Table 8-17 and Table 8B-1 in

11   Appendix 8B). Of particular relevance are two new multi-city studies (Schwartz, 1999; Samet

12   et al., 2000a,b; Zanobetti et al., 2000a), which provide evidence substantiating significant PM

13   effects on cardiovascular-related hospital admissions and visits. Numerous other studies, carried

14   out by individual investigators in a variety of locales, present a more varied picture, especially

15   when gaseous co-pollutants have been analyzed on equal footing with PM.

16   For example, Schwartz (1999) extended the analytical approach he had used in Tucson

17   (described below) to eight more U.S. metropolitan areas, limiting analyses to a single county in

18   each location to enhance representativeness of the air pollution data. The locations analyzed

19   were: Chicago, IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN;

20   Seattle, WA; Spokane, WA; and Tacoma, WA. Again, the analyses focused on total

21   cardiovascular (CVD) hospital admissions among persons $\geq$65 years old. In univariate

22   regressions, remarkably consistent PM_{10} associations with CVD admissions were found across

23   the eight locations, with a 50 μg/m^3 increase in PM_{10} associated with 3.6 to 8.6% increases in

24   admissions. The univariate eight-county pooled PM_{10} effect was 5.0% (CI 3.7-6.4), similar to the

25   6.1 % effect per 50 μg/m^3 observed in the previous Tucson analysis. In a bivariate model that

26   included CO, the pooled PM_{10} effect size diminished somewhat to 3.8% (CI 2.0-5.5) and the CO

27   association with CVD admissions was generally robust to inclusion of PM_{10} in the model.

28   Additional new results were based on analyses of daily CVD hospital admissions in persons

29   65 and older in relation to PM_{10} in 14 cities from the NMMAPS multi-city study (Samet et al.,

30   2000a,b). Cities included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado

31   Springs, CO; Detroit, MI; Minneapolis/ St. Paul, MN; Nashville, TN; New Haven, CT;

TABLE 8-17. SUMMARY OF STUDIES OF PM_{10} OR $PM_{2.5}$ AND TOTAL CVD HOSPITAL VISITS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (IQR) $\mu g/m^3$	Co-pollutants Analyzed with PM	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} or 25 $\mu g/m^3$ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-pollutants					
Samet et al. (2000a,b) 14 Cities	Total CVD admiss. $\geq$ 65 yrs	Mean 24.4-45.3	none	0 day	5.5% (4.7, 6.2)
Schwartz (1999) 8 Counties	Total CVD admiss. $\geq$ 65 yrs	Median 23-37	none	0 day	5.0% (3.7, 6.4)
Linn et al. (2000) Los Angeles	Total CVD admiss. $\geq$ 30 yrs	45, 18	none	0 day	3.25% (2.04, 4.47)
Schwartz (1997) Tucson, AZ	Total CVD admiss. $\geq$ 65 yrs	42, IQR 23	none	0 day	6.07% (1.12, 1.27)
Gwynn et al. (2000) Buffalo, NY	CVD HA	mn/max 24.1/90.8	none	3 day	5.7% (-3.3, 15.5)
Moolgavkar (2000b) Cook County, IL	Total CVD admiss. $\geq$ 65 yrs	35, IQR 22	none	0 day	4.2% (3.0, 5.5)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admiss. $\geq$ 65 yrs	44, IQR 26	none	0 day	3.2% (1.2, 5.3) 4.3% (2.5, 6.1)*
Moolgavkar (2000b) Maricopa County, AZ	Total CVD admiss. $\geq$ 65 yrs	41, IQR 19	none	0 day	$-$2.4% (-6.9, 2.3)
Zanobetti et al., 2000a Cook County, IL	Total CVD admiss. $\geq$ 65 yrs	Median 33, IQR 23	none	0-1 day avg.	6.6% (4.9, 8.3)
Tolbert et al., (2000a) Atlanta, GA 1993-1998	Total CVD emerg. dept. visits, $\geq$ 16 yrs	30.1, 12.4 Period 1	none	0-2 day avg.	$-$8.2% (p=0.002)
Tolbert et al., (2000a) Atlanta, GA 1998-1999	Total CVD emerg. dept. visits, $\geq$ 16 yrs	29.1, 12.0 Period 2	none	0-2 day avg.	5.1% (-7.9, 19.9) 6.1% (-3.1, 16.2)* 17.6% (-4.6, 45.0)**
U.S. Results With Co-pollutants					
Schwartz (1999) 8 Counties	Total CVD admiss. $\geq$ 65 yrs	Median 23-37	CO	0 day	3.8% (2.0, 5.5)
Schwartz (1997) Tucson, AZ	Total CVD admiss. $\geq$ 65 yrs	42, IQR 23	CO	0 day	5.22% (0.17, 10.54)

TABLE 8-17 (cont'd). SUMMARY OF STUDIES OF PM$_{10}$ OR PM$_{2.5}$ AND TOTAL CVD HOSPITAL VISITS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (IQR)	Co-pollutants Analyzed with PM	Lag Structure	Effect measures standardized to 50 μg/m^3 PM$_{10}$ or 25 μg/m^3 PM$_{2.5}$*
U.S. Results With Co-pollutants (cont'd)					
Moolgavkar (2000b) Cook County, IL	Total CVD admiss. ≥ 65 yrs	35, IQR 22	NO2	0 day	1.8% (0.4, 3.2)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admiss. ≥ 65 yrs	44, IQR 26	none	0 day	−1.8% (-4.4, 0.9) 0.8% (-1.3, 2.9)*
Non-U.S. Results Without Co-pollutants					
Burnett et al., (1997a) Toronto, Canada	Total CVD admiss. all ages	28, IQR 22	none	1-4 day avg.	7.7% (0.9, 14.8) 5.9% (1.8, 10.2) PM$_{2.5}$* 13.5% (5.5, 22.0)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	14.0, 9.0	none	1-3 day avg.	29.3% (p=0.003) 14.4% (p = 0.055) PM$_{2.5}$*
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admiss. ≥ 65 yrs	28.5, 90-10 %tile range: 30.7	none	0 day	2.5% (-0.2, 5.3)
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admiss. ≥ 65 yrs	20.7, 8.4	none	1-3 day avg.	12.4% (4.6, 20.9)
Wong et al. (1999)	Total emerg. CVD admiss. ≥ 65 yrs	Median 45.0, IQR 34.8	none	0-2 day avg.	4.1% (1.3, 6.9)
Non-U.S. Results With Co-pollutants					
Burnett et al., (1997a) Toronto, Canada	Total CVD admiss. all ages	28, IQR 22	O$_3$, NO$_2$, SO$_2$, CO	1-4 day avg.	−0.9% (-8.3, 7.1) −1.1% (−7.8, 6.0) PM$_{2.5}$* 8.1% (-1.3, 18.3)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	14.0, 9.0	CO, H$_2$S, NO$_2$, O$_3$, SO$_2$, total reduced sulfur	1-3 day avg.	PM$_{10}$ not significant; no quantitative results presented
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admiss. ≥65 yrs	28.5, 90-10 %tile range: 30.7	NO$_2$, O$_3$, SO$_2$, CO	0 day	PM$_{10}$ not significant; no quantitative results presented
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admiss. ≥ 65 yrs	20.7, 8.4	SO$_2$, NO$_2$, O$_3$, CO	1-3 day avg.	PM$_{10}$ effect robust; no quantitative results presented
Wong et al. (1999)	Total emerg. CVD admiss. ≥ 65 yrs	Median 45.0, IQR 34.8	NO$_2$, O$_3$, SO$_2$	0-2 day avg.	PM$_{10}$ effect robust; no quantitative results presented

*PM$_{2.5}$ entries. **PM$_{10-2.5}$. All others relate to PM$_{10}$.

1   Pittsburgh, PA; Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range

2   of years studied encompassed 1985-1994, although this varied by city. Covariates included SO_2,

3   NO_2, O_3, and CO; however these were not analyzed directly as regression covariates. Individual

4   cities were analyzed first by Poisson regression methods on PM_{10} for lags from 0 to 5 days.

5   An overall PM_{10} risk estimate was then computed by taking the inverse-variance weighted mean

6   of the city-specific risk estimates. The city-specific risk estimates for PM_{10} were also examined

7   for correlations with omitted covariates, including other pollutants. No relationship was

8   observed between city-specific risk estimates and measures of socioeconomic status, including

9   percent living in poverty, percent non-white, and percent with college educations. The overall

10   weighted mean risk estimate for PM_{10} was greatest for lag 0 and for the mean of lags 0-1.

11   For example, the mean risk estimate for the mean of lags 0-1 was a 6.0% increase in CVD

12   admissions per 50 $\mu g/m^3$ PM_{10} (95% CI: 5.1 - 6.8). The mean risk was larger in a subgroup of

13   data where PM_{10} was less than 50 $\mu g/m^3$, suggesting the lack of a threshold. A weakness of this

14   study was its failure to report multipollutant results. The authors argued that confounding by

15   co-pollutants was not present because the city-specific risk estimates did not correlate with city-

16   specific regressions of PM_{10} on co-pollutant levels. However, the validity of this method for

17   identifying meaningful confounding by co-pollutants at the daily time-series level has not been

18   demonstrated. Thus, it is not possible to conclude from these results alone that the observed

19   PM_{10} associations were independent of co-pollutants.

20   Janssen et al. (2002), in further analyses of the data set examined above by Samet et al.

21   (2000a,b), evaluated whether differences in prevalence in air conditioning (AC) and/or the

22   contribution of different sources to total PM_{10} emissions could partially explain the observed

23   variability in exposure-effect relations in the 14 cities. Cities were characterized and analyzed as

24   either winter or nonwinter peaking for the AC analyses. Data on the prevalence of AC from the

25   1993 American Housing Survey of the United States Census Bureau (1995) were used to

26   calculate the percentage of homes with central AC for each metropolitan area. Data on PM_{10}

27   emissions by source category were obtained by county from the U.S. EPA emissions and air

28   quality data web site (2000). In an analysis of all 14 cities, central AC was not strongly

29   associated with PM_{10} coefficients. However, separate analysis for nonwinter peaking and winter

30   peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased

31   significantly with increased percentage of central AC for both groups of cities, as shown in

1   Figure 8-11a. Another plot shown in Figure 8-11b depicts the relationships between PM_{10}

2   percent emissions from highways and CVD, showing significant positive relationships. For both

3   analyses, similar patterns were found for hospitalization for COPD and pneumonia. The authors

4   note that the stronger relationship for hospital admission rates for CVD over COPD and

5   pneumonia may relate to the 10 times higher CVD hospital admissions rate (which would result

6   in less error). However, no co-pollutant analyses were reported. The ecologic nature and limited

7   sample size also indicate the need for further study.

8   Zanobetti et al. (2000a) re-analyzed a subset of 10 cities from among the 14 evaluated by

9   Samet et al. (2000a,b). The same basic pattern of results obtained by Samet et al. (2000a,b) were

10   found, with strongest PM_{10} associations on lag 0 day, smaller effects on lag 1 and 2, and none at

11   longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (95%

12   CI 4.7, 6.4) per 50 μg/m^3 PM_{10} increment. The 0-1 day lag average excess CVD risk = 6.2%

13   (95% CI 5.4, 7.0) per 50 μg/m^3 PM_{10} increment. Effect size estimates increased when data were

14   restricted to days with PM_{10} < 50 μg/m^3. As before, no evidence of gaseous (CO, O_3, SO_2)

15   co-pollutant modification of PM effects was seen in the second stage analyses. Again, however,

16   co-pollutants were not tested as independent explanatory variables in the regression analysis.

17   Turning to some examples of independent single-city analyses, PM_{10} associations with

18   CVD hospitalizations were also examined in a study by Schwartz (1997), which analyzed three

19   years of daily data for Tucson, AZ linking total CVD hospital admissions for persons $\geq$ 65 years

20   old with PM_{10}, CO, O_3, and NO_2. As was the above case in Chicago, only one site monitored

21   daily PM_{10}, whereas multiple sites did so for gaseous pollutants (O_3, NO_2, CO). Both PM_{10} and

22   CO were independently (i.e., robustly) associated with CVD-related admissions, whereas O_3 and

23   NO_2 were not. The percent effect of a 50 μg/m^3 increase in PM_{10} changed only slightly from 6.07

24   (CI 1.12-11.27) to 5.22 (CI 0.17 - 10.54) when CO was included in the model along with PM_{10}.

25   Morris and Naumova (1998) reported results for PM_{10}, as well as for O_3, NO_2, and SO_2 in

26   an analysis of four years of congestive heart failure data among people $\geq$ 65 years old in Chicago,

27   IL. As many as eight monitoring sites were available for calculating daily gaseous pollutant

28   concentrations; however, only one site in Chicago monitored daily PM_{10}. Only same-day results

29   were presented, based on an initial exploratory analysis showing strongest effects for same-day

30   pollution exposure (i.e., lag 0). Associations between hospitalizations and PM_{10} were observed

31   in univariate regressions (3.9% [1.0, 6.9] per 50 μg/m^3 PM_{10} increase), but these diminished
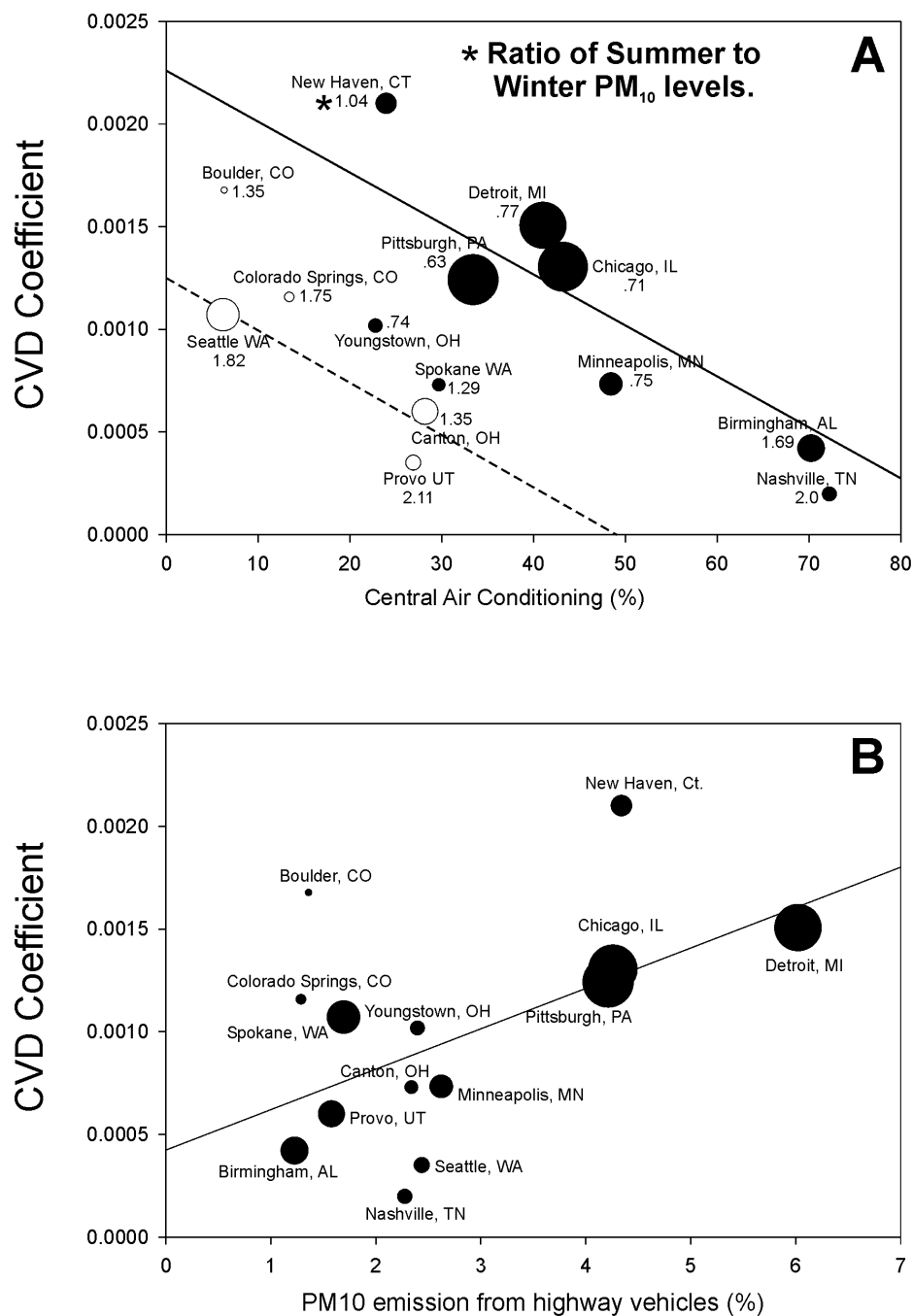
Figure 8-11. Univariate relation between percentage of homes with central AC and regression coefficients for (A) CVD, for cities nonwinter peaking PM$_{10}$ concentrations (solid line) and winter peaking PM$_{10}$ concentrations (dashed line) and (B) univariate relation between percentage of PM$_{10}$ from highway vehicles and regression coefficients for CVD. Circle area is proportional to the inverse of the variance of the effect estimate. Lines represent inverse variance regression equations (fixed-effects model).

Source: Adapted by EPA from Janssen et al. (2002).

1   somewhat in a multi-pollutant model (2.0%, [−1.4, 5.4]). Strong, robust associations were seen

2   between CO and congestive heart failure admissions. These results seem to suggest a more

3   robust association with CO than with PM_{10}. However, the observed differences might also be

4   due in part to differential exposure misclassification for PM_{10} (monitored at one site) as

5   compared with CO (eight sites).

6   In one of two U.S. studies comparing multiple PM indices, Lippmann et al. (2000)

7   analyzed associations between PM_{10}, $PM_{2.5}$, or $PM_{10\text{-}2.5}$ and various categories of CVD hospital

8   admissions among the elderly (65+ yr) in Detroit on 490 days in the period 1992-1994. The most

9   striking findings were notable percent excess risk for: (a) ischemic heart disease (IHD) in

10   relation to PM indices, i.e. 8.9% (0.5, 18.0) per 50 μg PM_{10}; 10.5% (2.8, 18.9) per 25 μg/m^3

11    $PM_{10\text{-}2.5}$; and 4.3% (−1.4, 10.4) per 25 μg/m^3 $PM_{2.5}$ (all at lag 2d); and (b) heart failure, i.e. 9.7%

12   (0.2, 20.1) per 50 μg/m^3 PM_{10}; 5.2% (−3.3, 14.5) per 25 μg/m^3 $PM_{10\text{-}2.5}$; and 9.1% (2.4, 6.2) per

13   25 μg/m^3 $PM_{2.5}$ (the first two at lag 0 d and the latter at lag 1 d). The PM effects generally were

14   robust when co-pollutants were added to the model. As discussed earlier with regard to the

15   Lippmann et al. (2000) mortality findings, it is difficult to discern whether the observed

16   associations with coarse fraction particles ($PM_{10\text{-}2.5}$) are independently due to such particles or

17   may possibly be attributed to the moderately correlated fine particle ($PM_{2.5}$) fraction in Detroit.

18   Also, power was limited by the small sample size.

19   Tolbert et al. (2000a) reported very preliminary results on multiple PM indices as they

20   relate to daily hospital emergency department visits for dysrhythmias (DYS) and all CVD

21   categories for persons aged 16 yrs or older, based on analyses of data from 18 of 33 participating

22   hospitals in an ongoing study in Atlanta. During Period 1 of the study (1993-1998), PM_{10} from

23   the EPA AIRS database was reported to be negatively associated with CVD visits. In a

24   subsequent one-year period (Aug. 1998 - Aug. 1999), when data became available from the

25   Atlanta PM supersite, positive but non-significant associations were seen between CVD and

26   PM10 (RR of 5.1% per 50 μg/m^3 PM_{10}) and PM2.5 (RR of 6.1% per 25 μg/m^3 $PM_{2.5}$); and

27   significant positive associations were seen with certain fine particle components, i.e., elemental

28   carbon (p ≤ 0.005) and organic carbon (p ≤ 0.02), along with CO (p ≤ 0.005). No multi-pollutant

29   results were reported. Study power was limited due to the short data record in Period 2.

30   In addition, caution applies to acceptance of the Tolbert et al. (2000a) findings until more

31   complete analyses from all participating hospitals are carried out and reported.

1   In an analysis of 1992-1995 Los Angeles data, Linn et al. (2000) also found that PM_{10}, CO,

2   and NO_2 were all significantly associated with increased cardiovascular admission in single-

3   pollutant models among persons aged 30 yr and older. Associations generally appeared to be

4   stronger for CO than for PM_{10}. No PM_{10} results were presented with co-pollutants in the model.

5   Lastly, Moolgavkar (2000b) analyzed PM_{10}, CO, NO_2, O_3, and SO_2 in relation to daily total

6   cardiovascular (CVD) and total cerebrovascular (CrD) admissions for persons aged ≥ 65 from

7   three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ) in the period 1987-1995.

8   Consistent with most studies, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) was associated at

9   some lags with CVD admissions in Cook and LA counties, but not in Maricopa county.

10   However, in two-pollutant models in Cook and LA counties, the PM risk estimates diminished

11   substantially and/or were rendered non-significant, whereas co-pollutant (CO or NO_2) risk

12   estimates were less affected. Results of this study suggest that gaseous pollutants, with the

13   exception of 0_3, were more strongly associated with CVD hospitalizations than was PM.

14   The above analyses of daily PM_{10} and CO in U.S. cities, overall, indicate that elevated

15   concentrations of both PM_{10} and CO may enhance risk of CVD-related morbidity leading to acute

16   hospitalizations. The Lippmann results appear to implicate $PM_{2.5}$ and/or $PM_{10-2.5}$ in increased

17   hospital admissions for some categories of CVD among the elderly.

18

19   ### 8.3.1.3.2 *Studies in Non-U.S. Cities*

20   Four separate analyses of hospitalization data in Canada have been reported by Burnett and

21   coworkers since 1995 (Burnett et al., 1995, 1997a,b, 1999). A variety of locations, outcomes,

22   PM exposure metrics, and analytical approaches were used in these studies, which hinders

23   somewhat the ability to draw broad conclusions across the full group. The first (Burnett et al.,

24   1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in

25   Ontario, CN. Cardiovascular (CVD) and respiratory hospital admissions were analyzed in

26   relation to sulfate and ozone concentrations. Sulfate lagged one day was associated with CVD

27   admissions, with a percent effect of 2.8 (CI 1.8-3.8) per 13 $\mu g/m^3$ without O_3 in the model and

28   3.3 (CI 1.7-4.8) with O_3 included. When CVD admissions were split out into sub-categories,

29   larger associations were seen between sulfates and coronary artery disease and heart failure than

30   for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the elderly

1   sub-population $\geq$ 65 yr old (3.5% per 13 μg/m^3) than for those <65 yr old (2.5% per 13 μg/m^3).

2   There was little evidence for seasonal differences in sulfate associations.

3   Burnett et al. (1997c) analyzed daily congestive heart failure hospitalizations in relation to

4   carbon monoxide and other air pollutants (O$_3$, NO$_2$, SO$_2$, CoH) in ten large Canadian cities as a

5   replication of an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study

6   expanded upon the previous work both by its size (11 years of data for each of 10 large cities)

7   and also by including a measure of PM air pollution (coefficient of haze, CoH), whereas no PM

8   data were included in the earlier Morris et al. study. The Burnett study was restricted to the

9   population $\geq$ 65 years old. The authors noted that all pollutants except O$_3$ were correlated,

10   making it difficult to separate them statistically. CoH, CO, and NO$_2$ measured on the same day

11   as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in

12   univariate models. In multi-pollutant models, CO remained a strong predictor, whereas COH did

13   not (gravimetric PM measures were not evaluated).

14   The roles played by size-selected gravimetric and chemically speciated particle metrics as

15   predictors of CVD hospitalizations were explored in analysis of data from metropolitan Toronto

16   for the summers of 1992-1994 (Burnett et al., 1997a). The analysis used dichotomous sampler

17   (PM$_{2.5}$, PM$_{10}$, and PM$_{10-2.5}$), hydrogen ion, and sulfate data collected at a central site as well as O$_3$,

18   NO$_2$, SO$_2$, CO, and COH data collected at multiple sites in Toronto. Hospital admissions

19   categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac

20   dysrhythmias, and heart failure) and total respiratory. Model specification with respect to

21   pollution lags was completely data-driven, with all lags and averaging times out to 4 days prior to

22   admission evaluated in exploratory analyses and "best" metrics chosen on the basis of maximal

23   t-statistics. The relative risks of CVD admissions were positive and generally statistically

24   significant for all pollutants analyzed in univariate regressions, but especially so for O$_3$, NO$_2$,

25   COH, and PM$_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants were

26   generally robust to inclusion of PM covariates, whereas the PM indices (aside from COH) were

27   not robust to inclusion of multiple gaseous pollutants. In particular, PM$_{2.5}$ was not a robust

28   predictor of CVD admissions in multi-pollutant models: whereas an 25 μg/m^3 increase in PM$_{2.5}$

29   was associated with a 5.9% increase (t=1.8) in CVD admissions in a univariate model, the

30   percent effect was reduced to -1.1 (t=0.3) in a model that included O$_3$, NO$_2$, and SO$_2$. COH, like

31   CO and NO$_2$, is generally thought of as a measure of primary motor-vehicle emissions during the

1   non-heating season. The authors concluded that "particle mass and chemistry could not be

2   identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this

3   study beyond that attributable to climate and gaseous air pollution."

4   Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-

5   specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air

6   pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out

7   into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease.

8   The analyses also examined several respiratory causes, as well as cerebrovascular and diseases of

9   the peripheral circulation (the latter categories being included because they should show PM

10   associations if one mechanism of PM action is related to increased plasma viscosity, as suggested

11   by Peters et al. (1997a). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ estimated from

12   daily TSP and TSP sulfate data, based on a regression analysis on dichotomous sampling data

13   that were available every sixth day during an eight-year subset of the full study period. This use

14   of estimated rather than measured PM components limits the interpretation of the PM results

15   reported here. In general, use of estimated PM exposure metrics will tend to increase exposure

16   measurement error and thereby tend to decrease effects estimates. Model specification for lags

17   was again data-driven, based on maximal t-statistics. Although some statistically significant

18   associations with one or another PM metric were found in univariate models, there were no

19   significant PM associations with any of the three CVD hospitalization outcomes in multi-

20   pollutant models. For example, whereas an 25 μg/m^3 increase in estimated $PM_{2.5}$ was associated

21   with a 8.05% increase (t-statistic = 6.08) in ischemic heart disease admissions in a univariate

22   analysis, the $PM_{2.5}$ association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in

23   the model. The gaseous pollutants dominated most regressions. There also were no associations

24   between PM and cerebral or peripheral vascular disease admissions.

25   The Burnett et al. studies provide some of the most extensive results for PM in conjunction

26   with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the various

27   analyses confuses the picture somewhat. A general finding appears to be lack of robustness of

28   associations between cardiovascular outcomes and PM in multi-pollutant analyses. This was

29   seen for COH in the analysis of 10 Canadian cities (Burnett et al., 1997c), for $PM_{2.5}$ and PM_{10} in

30   the analysis of summer data in Toronto (Burnett et al., 1997a), and for linear combinations of

31   TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in

1   Toronto (Burnett et al., 1999). One exception was the association reported between CVD

2   admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the

3   sulfate association was robust to the inclusion of O_3. Also, although gravimetric PM variables

4   were not robust predictors in the Toronto summer analysis, COH was (Burnett et al., 1997a),

5   perhaps reflecting the impact of primary motor vehicle emissions. This contrasts, however, with

6   COH's lack of robustness in the 10-city analysis (Burnett et al., 1997c).

7   Stieb et al. studied all-age acute cardiac emergency room visits in relation to a rich set of

8   pollution covariates in Saint John, Canada for the period 1992-1996. Daily data were available

9   on $PM_{2.5}$, PM_{10}, fine fraction hydrogen and sulfate ions, COH, CO, H_2S, NO_2, O_3, SO_2, and total

10   reduced sulfur. In a multi-pollutant model, neither PM_{10} nor $PM_{2.5}$ were significantly related to

11   total cardiac ED visits, though O_3 and SO_2 were.

12   Several additional non-U.S. studies, mainly in the U.K., have also been published since the

13   1996 PM AQCD. Most of these studies evaluated co-pollutant effects along with those of PM.

14   Interpretation is hindered somewhat, however, by the failure to report quantitative results for

15   PM_{10} in the presence of co-pollutants. In univariate models, Atkinson et al. (1999a) reported

16   significant associations of both ambient PM_{10} and black smoke (BS), as well as all other

17   co-pollutants, with daily admissions for total cardiovascular disease and ischemic heart disease

18   for 1992-1994 in London, UK, using standard time series regression Methods. Co-pollutants

19   included NO_2, O_3, SO_2, and CO. PM associations were observed for persons aged < 65 yr and for

20   persons aged ≥ 65 yr. In two-pollutant models, the associations with PM_{10}, NO_2, SO_2, and CO

21   were moderated by the presence of BS in the model, but the BS association was robust to

22   co-pollutants. Interpretation is hampered somewhat by the lack of quantitative results for

23   two-pollutant models. In another U.K. study, associations with PM_{10}, and to a lesser extent BS,

24   SO_2, and CO, were reported for analyses of daily emergency hospital admissions for

25   cardiovascular diseases from 1992-1995 for Edinburgh, UK (Prescott et al., 1998).

26   No associations were observed for NO_2 and ozone. Significant PM_{10} associations were present

27   only in persons 65 and older. The authors reported that the PM_{10} associations were unaffected by

28   inclusion of other pollutants; however, results were not shown. On the other hand, no

29   associations between PM_{10} and daily ischemic heart disease admissions were observed by

30   Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK.

31   However, PM_{10} was associated with respiratory admissions and cardiovascular mortality during

1 the same study period. This inconsistency of results across causes and outcomes is difficult to

2 interpret, but may relate in part to the relatively short time series analyzed. The authors stated

3 that gaseous pollutants did not have significant associations with health outcomes independent of

4 PM, but no results were presented for models involving gaseous pollutants.

5 In eight European cities, the APHEA II (Le Tertre et al., 2002) project examined the

6 association between PM_{10} and hospital admissions for cardiac causes. They found a significant

7 effect of PM_{10} (0.5%; 0.2, 0.8) on admission for cardiac causes (all ages) and cardiac causes

8 (0.7%; 0.4, 1.0) and ischemic heart disease (0.8%; 0.3, 1.2) for people over 65 years with the

9 impact of PM_{10} per unit of pollution being half that found in the United States. PM_{10} did not

10 seem to be confounded by O_3 and SO_2. The PM_{10} effect was reduced when CO was incorporated

11 in the regression model and eliminated when controlling for NO_2.

12 A study in Hong Kong by Wong et al (1999) found associations between CVD admissions

13 and PM_{10}, SO_2, NO_2, and O_3 in univariate models, but did not examine multi-pollutant models.

14 Ye and colleagues analyzed a 16 year record of daily emergency hospital visits for July and

15 August in Tokyo among persons age 65 and older (Ye et al., 2001). In addition to PM_{10}, the

16 study included NO_2, ozone, SO_2, and CO. Models were built using an objective significance

17 criterion for variable inclusion. NO_2 was the only pollutant significantly associated with angina,

18 cardiac insufficiency, and myocardial infarction hospital visits.

19

20 *8.3.1.3.3 Summary and Conclusions*

21 The ecologic time series studies reviewed here add substantially to the body of available

22 literature on acute CVD morbidity effects of PM and co-pollutants. Two U.S. multi-city studies

23 offer the strongest current evidence for effects of PM_{10} on acute CVD hospital admissions.

24 However, uncertainties regarding the possible role of co-pollutants in the larger of the two

25 studies hinders interpretation with respect to independent PM_{10} effects. Among single-city

26 studies carried out in the U.S. and elsewhere by a variety of investigators (see Summary

27 Table 8-17), less consistent evidence for PM effects is seen. Of particular importance is the

28 possible roles of co-pollutants (e.g., CO) as confounders of the PM effect. Among

29 13 independent studies that included gravimetrically-measured PM_{10} and co-pollutants, three

30 reported PM effects that appeared independent of co-pollutants (Schwartz, 1997; Lipmmann

31 et al., 2000; Prescott et al., 1998), eight reported no significant PM_{10} effects after inclusion of

1   co-pollutants (Morris and Naumova, 1998; Moolgavkar, 2000b; Tolbert et al., 2000a; Burnett

2   et al., 1997a; Steib et al., 2000; Atkinson et al., 1999b; Wordley et al. (1997); Morgan et al.,

3   1998; Ye et al., 2001), and two studies were unclear regarding independent PM effects (Linn

4   et al., 2000; Wong et al., 1999). In a recent quantitative review of published results from

5   12 studies on airborne particles and hospital admissions for cardiovascular disease, Morris

6   (2001) noted that adjustment for co-pollutants consistently reduced the PM_{10} effect, with

7   reductions ranging from 10 to 320% across studies. Thus, although several studies appear to

8   provide evidence for PM effects on CVD hospital admissions independent of co-pollutant

9   effects, still other studies examining co-pollutants yield results, showing PM effects in some

10   studies while not in others.

11   With respect to the question of particle size, only a handful of studies have examined the

12   relative impacts of different particle indicators (Lippmann et al., 2000, Burnett et al., 1997a,

13   Tolbert et al., 2000a, Steib et al., 2000, Moolgavkar, 2000b). Perhaps due to statistical power

14   issues, no clear picture has emerged as to the particle size fraction most associated with acute

15   CVD effects.

16   Because hospitalization can be viewed as a less severe manifestation of the same

17   pathophysiologic mechanism that may be responsible for acute mortality following PM exposure,

18   it is of interest to assess the coherence between the morbidity results reviewed here and the

19   mortality results reviewed in Section 8.2.2 (Borja-Aburto et al., 1997, 1998; Braga et al., 2001;

20   Goldberg et al., 2000; Gouveia and Fletcher, 2001; Hoek et al., 2001; Kwon et al., 2001;

21   Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson

22   et al., 1997; Wordley et al., 1997; Zeghnoun et al., 2001; Zmirou et al., 1998). The mortality

23   studies reported significant associations between acute CVD mortality and measures of ambient

24   PM, though the PM metrics utilized and the relative risk estimates varied across studies. PM

25   measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$,

26   $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and

27   black smoke (filter reflectance). Where tested, PM associations with acute CVD mortality

28   appeared to be generally more robust to inclusion of gaseous covariates than was the case for

29   acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998; Wordley

30   et al., 1997; Zmirou et al., 1998). One study (Goldberg et al., 2000) which examined multiple

31   alternative PM metrics reported strongest associations with $PM_{2.5}$ and no associations for $PM_{10-2.5}$

1   and hydrogen ion. Three studies (Braga et al., 2001; Goldberg et al., 2000; Hoek et al., 2001),

2   as noted in Section 8.2.2, provide data indicating that some specific cardiovascular causes of

3   mortality (such as heart failure) were more strongly associated with air pollution than total

4   cardiovascular mortality; but it was noted that ischemic heart disease (which contributes about

5   half of all CVD deaths) was the strongest contribution to the association between air pollution

6   and cardiovascular mortality. These results for acute cardiovascular mortality are qualitatively

7   consistent with those reviewed above for hospital admissions.

8   Figure 8-12 illustrates PM_{10} excess risk estimates for single-pollutant models derived from

9   selected U.S. studies of PM_{10} exposure and total cardiovascular disease (CVD) hospital

10   admissions, standardized to a 50 $\mu g/m^3$ exposure to PM_{10}. Results are shown both for studies

11   yielding pooled outcomes for multiple U.S. cities and for studies of single U.S. cities. The Samet

12   et al. (2000a) pooled cross-city results for 14 U.S. cities provides the most precise estimate for

13   relationships of U.S. ambient PM_{10} exposure to increased risk for CVD hospitalization. That

14   estimate, and those derived from most other studies depicted in Figure 8-6, generally appear to

15   confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of

16   3-10% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$65 yr).   Also, other individual-city

17   results from Detroit are indicative of excess risk for ischemic heart disease and heart failure in

18   the range of approximately 4.0 to 10.0% per 25 $\mu g/m^3$ of $PM_{2.5}$ or $PM_{10-2.5}$, as are preliminary

19   individual-city findings from Atlanta suggestive of 4.3% and 10.5% excess risk per 25 $\mu g/m^3$ of

20   $PM_{2.5}$ and $PM_{10-2.5}$, respectively. However, the extent to which PM affects CVD hospitalization

21   risk independently of or together with other co-pollutants (such as CO), remains to be further

22   resolved.

23

24   *8.3.1.3.4 Individual-Level Studies of Cardiovascular Physiology*

25   New studies carried out by various groups have evaluated longitudinal associations

26   between ambient PM and physiologic measures of cardiovascular function or biochemical

27   changes in the blood that may be associated with *cardiac risks*. In contrast to the ecologic time-

28   series studies discussed above, these studies measure outcomes and most covariates at the

29   individual level, making it possible to draw conclusions regarding individual risks, as well as to

30   explore mechanistic hypotheses. Heterogeneity of responses across individuals, and across

31   subgroups defined on the basis of age, sex, pre-existing health status, etc., also can in principle
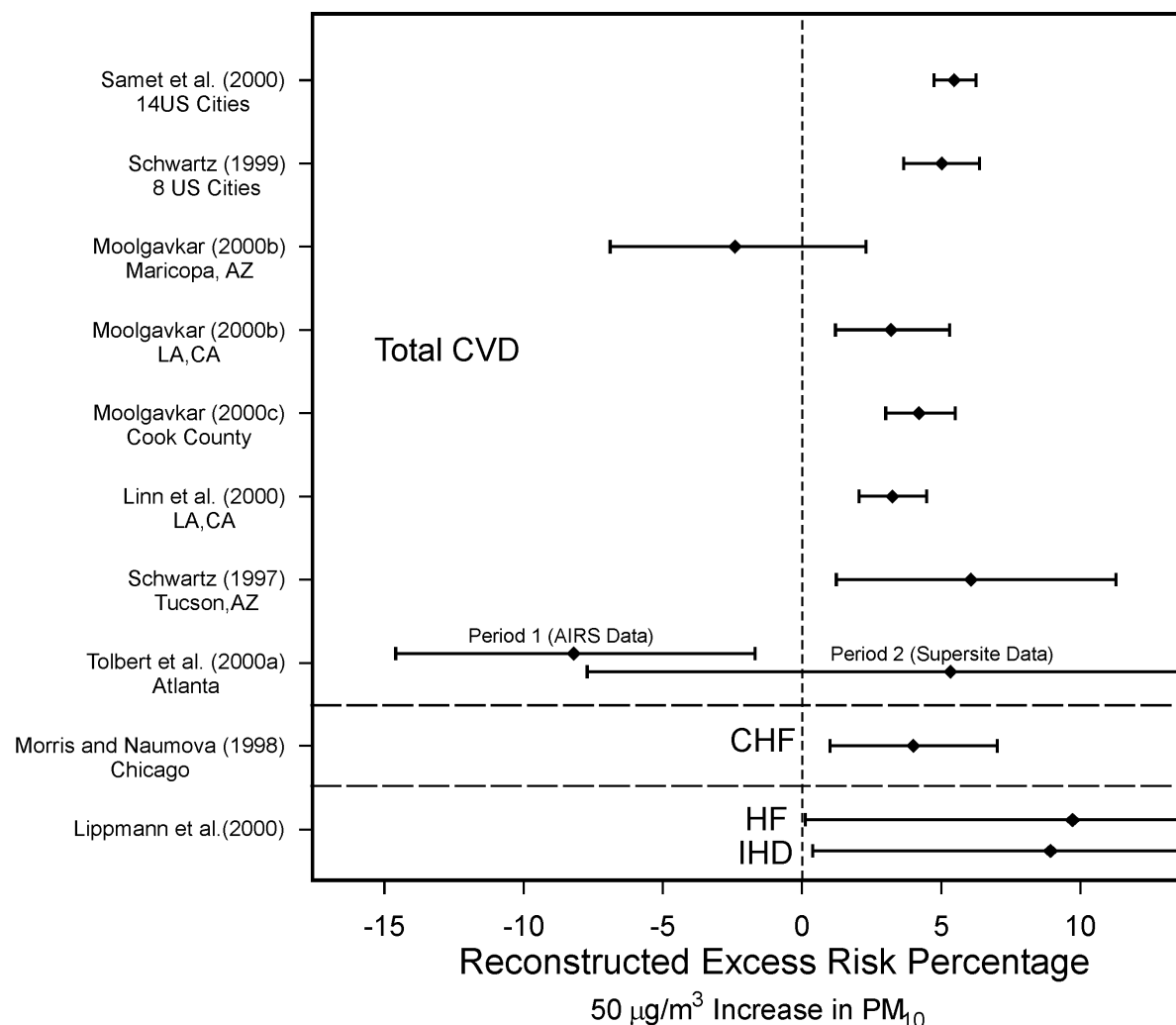
Figure 8-12. **Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from selected U.S. PM$_{10}$ studies. CVD = cardiovascular disease. CHF = congestive heart failure.**

1   be assessed. While exposure assessment remains largely ecologic (i.e., the entire population is

2   usually assigned the same exposure value on a given day), exposure is generally well

3   characterized in the small, spatially-clustered study populations. The recent studies fall into two

4   broad classes: those addressing cardiac rhythm or adverse events, and those addressing blood

5   characteristics. While significant uncertainty still exists regarding the interpretation of results

6   from these new studies, the varied responses that have been reported to be associated with

7   ambient PM and co-pollutants are of much interest in regard to mechanistic hypotheses

1 concerning pathophysiologic processes potentially underlying CVD-related mortality/morbidity

2 effects discussed in preceding sections.

3

4 *Cardiac Physiology and Adverse Cardiac Events*

5 Alterations in heart rate and/or rhythm have been hypothesized as possible mechanisms by

6 which ambient PM exposures may exert acute effects on human health. Decreased heart rate

7 variability, in particular, has been identified as a predictor of increased cardiovascular morbidity

8 and mortality. Several independent studies have recently reported temporal associations between

9 PM exposures and various measures of heart beat rhythm in panels of elderly subjects (Liao

10 et al., 1999; Pope et al., 1999a,b,c; Dockery et al., 1999; Peters et al., 1999a, 2000a; Gold et al.

11 2000; Creason et al., 2001). Changes in blood pressure may also reflect increases in risk (Linn

12 et al., 1999; Ibald-Mulli et al., 2001). Finally, one important new study has linked acute (2- and

13 24-h) ambient $PM_{2.5}$ and PM_{10} concentrations with increased risk of myocardial infarction in

14 subsequent hours and days (Peters et al., 2001).

15 Liao and colleagues (1999) studied 26 elderly subjects (age 65-89 years; 73% female) over

16 three consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were

17 classified as "compromised" based on previous cardiovascular conditions (e.g., hypertension).

18 Daily six-minute resting electrocardiogram (ECG) data were collected, and time intervals

19 between sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval

20 data to separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and

21 high frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N–N; also

22 designated R-R) heartbeat intervals (SDNN) was computed for use as a time-domain outcome

23 variable. $PM_{2.5}$ was monitored indoors by TEOM and outdoors by dichotomous sampler.

24 Outdoor $PM_{2.5}$ levels ranged from 8.0 to 32.2 $\mu g/m^3$ (mean = 16.1 $\mu g/m^3$). Regression analyses

25 controlled for inter-subject differences in average variability, allowing each subject to serve as

26 his/her own control. Consistent associations were seen between decreases in all three outcome

27 variables (LF, HF, SDNN) and increases in $PM_{2.5}$ concentrations (both indoors and outdoors),

28 with associations being stronger for the 18 "compromised"subjects. No analyses of heart rate

29 were reported.

30 Creason and colleagues (2001) recently reported results of a subsequent study using similar

31 methods among 56 elderly residents of a retirement center in Baltimore County, MD. The

1   11 men and 45 women ranged in age from 72 to 97 years and were all Caucasian. Associations

2   between decreased HRV and ambient $PM_{2.5}$ were again observed, though not significant at the

3   0.05 level and smaller in magnitude than in the previous Baltimore study. When two episodic

4    $PM_{2.5}$ days with rainfall were excluded from the 24-day data set, the $PM_{2.5}$ associations increased

5   in magnitude and became statistically significant. There was no evidence of larger effects among

6   subsets of subjects with compromised health status. No results were presented for other

7   pollutants besides $PM_{2.5}$.

8   Pope and colleagues (1999c) reported similar findings in a panel of six elderly subjects

9   (69-89 years, 5/6 male) with histories of cardiopulmonary disease, and one 23-year old male

10   subject suffering from Crohn's disease and arrhythmias. Subjects carried Holter monitors for up

11   to 48 hours during different weeks that varied in ambient PM_{10} concentrations. N-N heartbeat

12   intervals were recorded and used to calculate several measures of heart rate variability in the time

13   domain: the standard deviation of N-N intervals (SDNN), which is a broad measure of both high

14   and low frequency variations; the standard deviation of the averages of N-N intervals in all five

15   minute segments (SDANN), which is a measure of ultra-low frequency variations; and the root

16   mean squared differences between adjacent N-N intervals (r-MSSD), which is a measure of high

17   frequency variations. Daily gravimetric PM_{10} data obtained from three sites in the study area

18   ranged from circa 10 $\mu g/m^3$ to 130 $\mu g/m^3$ during the study. A simple step function in

19   concentration was observed with high levels occurring only during the first half of the 1.5 month

20   study period. Regression analysis with subject-specific intercepts was performed, with and

21   without control for daily barometric pressure and mean heart rate. Same-day, previous-day, and

22   the two-day mean of PM_{10} were considered. SDNN and SDANN were negatively associated with

23   both same-day and previous-day ambient PM_{10}, and results were unaffected by inclusion of

24   covariates. Heart rate, as well as r-MSSD, were both positively, but less strongly, associated

25   with PM_{10}. No co-pollutants were studied.

26   The Pope et al. (1999c) study discussed above was nested within a larger cohort of

27   90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley

28   (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in

29   oxygen saturation might occur as a result of PM exposure, and that this could be a risk factor for

30   adverse cardiac outcomes. The study was carried out in winter months (mid November through

31   mid-March), when frequent inversions lead to fine particle episodes. PM_{10} levels at the three

1   nearest sites averaged from 35 to 43 $\mu g/m^3$ during the study, with daily 24-h levels ranging from

2   5 to 147 $\mu g/m^3$. Two populations were studied: 52 retired Brigham Young University

3   faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO_2) and

4   heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger.

5   In regression analyses that controlled for inter-individual differences in mean levels, SpO_2 was

6   not associated with PM_{10}, but was highly associated with barometric pressure. In contrast, HR

7   significantly increased in association with PM_{10} and significantly decreased in association with

8   barometric pressure in joint regressions. Including CO in the regressions did not change these

9   basic findings. This was the first study of this type to examine the interrelationships among

10   physiologic measures (i.e., SpO_2 and HR), barometric pressure, and PM_{10}. The profound

11   physiological effects of barometric pressure noted here highlight the importance of carefully

12   controlling for barometric pressure effects in studies of cardiac physiology.

13   Gold and colleagues (2000) obtained somewhat different results in a study of heart rate

14   variability among 21 active elderly subjects, aged 53-87 yr, in a Boston residential community.

15   Resting, standing, exercising, and recovering ECG measurements were performed weekly using a

16   standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG

17   monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for

18   definitions). Heart rate also was analyzed as an outcome. Continuous PM_{10} and $PM_{2.5}$

19   monitoring was conducted by TEOM at a site 6 km from the study site, with PM data corrected

20   for loss of semivolatile mass. Data on CO, O_3, NO_2, SO_2, temperature and relative humidity

21   were available from nearby sites. Outcomes were regressed on $PM_{2.5}$ levels in the 0-24 hour

22   period prior to ECG testing, with and without control for HR and temperature. As for the other

23   studies discussed above, declines in SDNN were associated with $PM_{2.5}$ levels, in this case

24   averaged over 4 hours. These associations reached statistical significance at the 0.05 level only

25   when all testing periods (i.e., resting, standing, exercise) were combined. In contrast to the above

26   studies, both HR and r-MSSD here were negatively associated with $PM_{2.5}$ levels (i.e., lower HR

27   and r-MSSD) when $PM_{2.5}$ was elevated. These associations were statistically significant overall,

28   as well as for several of the individual testing periods, and were unaffected by covariate control.

29   Peters and colleagues (1999a) reported HR results from a retrospective analysis of data

30   collected as part of the MONICA study (monitoring of trends and determinants in cardiovascular

31   disease) carried out in Augsburg, Germany. Analyses focused on 2,681 men and women aged

1   25-64 years who had valid ECG measurements taken in winter 1984-1985 and again in winter

2   1987-1988. Ambient pollution variables included TSP, SO_2, and CO. The earlier winter included

3   a 10-day episode with unusually high levels of SO_2 and TSP, but not of CO. Pollution effects

4   were analyzed in two ways: dichotomously comparing the episode and non-episode periods, and

5   continuously using regression analysis. However, it is unclear from the report to what extent the

6   analyses reflect between-subject vs. within-subject effects. A statistically significant increase in

7   mean heart rate was observed during the episode period versus other periods, controlling for

8   cardiovascular risk factors and meteorology. Larger effects were observed in women. In single-

9   pollutant regression analyses, all three pollutants were associated with increased HR.

10   In another retrospective study, Peters and colleagues (2000a) examined incidence of cardiac

11   arrhythmias among 100 patients (mean age 62.2 yr.; 79% male) with implanted cardioverter

12   defibrillators followed over a three year period. $PM_{2.5}$ and PM_{10} were measured in South Boston

13   by the TEOM method, along with black carbon, O_3, CO, temperature and relative humidity; SO_2

14   and NO_2 data were obtained from another site. The 5th percentile, mean, and 95th percentiles of

15   PM_{10} concentrations were 7.8, 19.3, and 37.0 $\mu g/m^3$, respectively. The corresponding values for

16    $PM_{2.5}$ were 4.6, 12.7, and 26.6 $\mu g/m^3$. Logistic regression was used to analyze arrhythmia events

17   in relation to pollution variables, controlling for between-person differences, seasons, day-of-

18   week, and meteorology in two subgroups: 33 subjects with at least one arrhythmia event; and

19   6 subjects with 10 or more arrhythmia events. In the larger subgroup, only NO_2 on the previous

20   day, and the mean NO_2 over five days, were significantly associated with arrhythmia incidence.

21   In patients with 10 or more events, the NO_2 associations were stronger. Also, some of the $PM_{2.5}$

22   and CO lags became significant in this subgroup. These results should be interpreted cautiously

23   given the large number of statistical tests performed.

24   Linn and colleagues (1999) reported associations between both diastolic and systolic blood

25   pressure and PM_{10} in a panel study of 30 Los Angeles residents with severe COPD. Recently,

26   Ibald-Mulli et al. (2001) reported similar findings from a study of blood pressure among 2607

27   men and women aged 25-64 years who participated in the MONICA study in Augsburg,

28   Germany. Systolic blood pressure increased on average during an episode of elevated TSP and

29   SO_2, but the effect disappeared after controlling for meteorological parameters including

30   temperature and barometric pressure. However, when TSP and SO_2 were analyzed as continuous

31   variables, both were associated with elevated systolic blood pressure, controlling for

1   meteorological variables. In two-pollutant models, TSP was more robust than SO_2. Further, the

2   TSP association was greater in the subgroups of subjects with elevated blood viscosity and heart

3   rates.

4   An exploratory study of a panel of COPD patients (Brauer et al., 2001) examined several

5   PM indicators in relation to CVD and respiratory health effects. The very low levels of ambient

6   particle (PM_{10} mean - 18[7] $\mu g/m^3$) and low variability in these levels plus the sample size of 16

7   limit the conclusions that can be drawn. Nevertheless, for cardiovascular endpoints, single-

8   pollutant models indicated that both systolic and diastolic BP decreased with increasing

9   exposure, but this is not statistically significant. Also, the size of the ambient PM_{10} effect

10   estimate for ΔFEV_1 was larger than the effect estimate for ambient $PM_{2.5}$ and personal $PM_{2.5}$ but

11   not statistically significant. While the quantitative health relationships outcome results are

12   inconclusive, the results related to PM indicators is informative while requiring future research.

13   This initial effort indicates that ambient PM_{10} consistently had the largest effect estimates while

14   models using personal exposure measurements did not show larger or more consistently positive

15   effect estimates relative to those using ambient exposure metrics.

16   An important study by Peters et al. (2001) reported associations between onset of

17   myocardial infarction and ambient PM (either PM_{10} or $PM_{2.5}$) in a cohort of 772 MI patients

18   studied in Boston, MA as part of the determinants of myocardial infarction onset study. Precise

19   information on the timing of the MI, obtained from patient interviews, was linked with

20   concurrent air quality data measured at a single Boston site. A case crossover design enabled

21   each Subject to serve as his/her own control. One strength of this study was its analysis of

22   multiple PM indices and co-pollutants, including real-time $PM_{2.5}$, PM_{10}, the PM_{10}-$PM_{2.5}$

23   difference, black carbon, Ozone, CO, NO_2, and SO_2. Only $PM_{2.5}$ and PM_{10} were significantly

24   associated with MI risk in models adjusting for season, meteorological parameters, and day of

25   week. Both the mean $PM_{2.5}$ concentration in the previous two hours and in the 24 hours lagged

26   one day were independently associated with MI, with odds ratios of 1.48 (1.09-2.02) for 25

27   ug/m3 and 1.62 (1.13-2.34) for 20 ug/m3, respectively. PM_{10} associations were similar. The

28   non-significant findings for other pollution metrics should be interpreted in the context of

29   potentially differing exposure misclassification errors associated with the single monitoring site.

30   The above studies present a range of intriguing findings suggesting possible effects of PM

31   on cardiac rhythm and adverse events. Four separate studies reported decreases in HR variability

1   associated with PM in elderly cohorts, although r-MSSD (a measure of high-frequency HR

2   variability) showed elevations with PM in one study (Pope et al., 1999a). Also, all of the studies

3   which examined HR found an association with PM; most reported positive associations, whereas

4   one (Gold et al., 2000) reported a negative relationship. However, variations in methods and

5   results across the studies argue for caution in drawing strong conclusions regarding PM effects

6   from them, especially in light of the complex intercorrelations which exist among measures of

7   cardiac physiology, meteorology, and air pollution (Dockery et al., 1999).

8

9   *Viscosity and Other Blood Characteristics*

10   Peters et al. (1997a) state that plasma viscosity is determined by fibrinogen and other large

11   asymmetrical plasma proteins such as immunoglobulin M and $\propto_2$-macroglobulin. They note that

12   in a cohort study of elderly men and women, fibrinogen concentrations were strongly related to

13   inflammatory markers such as neutrophil count and acute-phase proteins, (C-reactive protein and

14    $\propto_1$-antichymotrypsin) and to self-reported infections. Fibrinogen contributes to plasma viscosity,

15   which is a risk factor for ischemic heart disease.

16   Support for a mechanistic hypothesis, relating to enhanced blood viscosity, is suggested in

17   an analysis of plasma viscosity data collected in a population of 3256 German adults in the

18   MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October

19   1984 to June 1985. An episode of unusually high air pollution concentrations occurred during a

20   13 day period while these measurements were being collected. The authors reported that, among

21   the 324 persons who provided blood during the episode, there was a statistically significant

22   elevation in plasma viscosity as compared with the 2932 persons studied at other times. The

23   odds ratio for plasma viscosity exceeding the 95th percentile was 3.6 (CI 1.6-8.1) among men

24   and 2.3 (CI 1.0-5.3) among women. Analysis of the distribution of blood viscosity data

25   suggested that these findings were driven by changes in the upper tail of the distribution rather

26   than by a general shift in mean viscosity, consistent with the likelihood of a susceptible

27   sub-population of individuals.

28   Peters et al. (2000b) reported on a prospective cohort study of a subset of male participants

29   from the above-described Augsburg, Germany MONICA study. Based on a survey conducted in

30   1984/85, a sample of 631 randomly selected men/aged 45-64 yr), free of cardiovascular disease at

31   entry, were evaluated in a 3-yr follow-up that examined relationships of air pollution to serum

1   C-reactive protein concentrations. C-reactive protein is a sensitive marker of inflammation,

2   tissue damage, and infections, with acute and chronic infections being related to coronary events,

3   as well as inflammation being related to systemic hypercoagulability and the onset of acute

4   ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and other parts

5   of Germany, the odds of abnormal increases in serum C-reactive protein (i.e., $\geq$90th percentile of

6   pre-episode levels = 5.7 mg/L) tripled and associated increases in TSP levels of 26 μg/m^3 (5-day

7   averages) were associated with an odds ratio of 1.37 (95% CI 1.08-1.73) for C-reactive protein

8   levels exceeding the 90th percentile levels in two pollutant models also including SO_2 levels.

9   The estimated odds ratio for a 30 μg/m^3 increase in the 5-day mean for SO_2 was 1.12 (95% CI

10   0.92 to 1.47; non-significant).

11   Two other recent studies also examined blood indices in relation to PM pollution (Seaton

12   et al., 1999; Prescott et al., 1999). Seaton and colleagues collected sequential blood samples (up

13   to 12) over an 18 month period in 112 subjects (all over age 60) in Belfast and Edinburgh, UK.

14   Blood samples were analyzed for hemoglobin, packed cell volumes, blood counts, fibrinogen,

15   factor VII, interleuken 6, C-reactive protein. In a subset of 60 subjects, plasma albumin also was

16   measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city.

17   Personal exposure estimates for the three days preceding each blood draw were derived from

18   ambient data adjusted by time-activity patterns and I/O penetration factors. No co-pollutants

19   were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons,

20   temperature, and between-subject differences. Significant changes in several of the blood indices

21   were observed in association with either ambient or estimated personal PM_{10} levels. All changes

22   were negative, except for C reactive protein in relation to ambient PM_{10}, which was positive.

23   Prescott et al. (1999) also investigated factors that might increase susceptibility to adverse

24   cardiovascular events resulting from PM exposure. Using data from a cohort of 1592 subjects

25   aged 55-74 in Edinburgh, UK, baseline measurements of blood fibrinogen and blood and plasma

26   viscosity were examined as modifiers of the effects of PM (indexed by BS) on the incidence of

27   fatal and non-fatal myocardial infarction or stroke. All three blood indices were strong predictors

28   of increased cardiac event risk. However, there was no clear evidence of either a main effect of

29   BS, nor interactions between BS and blood indices.

30   Two other new studies examined air pollution associations with plasma fibrinogen.

31   Pekkanen and colleagues (2000) analyzed plasma fibrinogen data from a cross-sectional survey

1 of 4982 male and 2223 female office workers in relation to same-day and previous three-days

2 concentrations of PM_{10}, black smoke, NO_2, CO, SO_2, and ozone. In the full analysis, NO_2 and

3 CO were significantly associated with fibrinogen levels. When the analysis was restricted to the

4 summer season, NO2 and CO, as well as PM_{10} and black smoke, showed significant univariate

5 associations. Schwartz (2001) reported significant associations between plasma fibrinogen levels

6 and PM_{10} exposures in a subset of the NHANES III cohort. PM_{10} associations also were

7 observed for platelet and white cell counts. The PM_{10} associations were robust when ozone,

8 NO_2, or SO_2 was included. CO was not analyzed.

9   The above findings add support for some intriguing hypotheses regarding possible

10 mechanisms by which PM exposure may be linked with adverse cardiac outcomes. They are

11 especially interesting in terms of implicating both increased blood viscosity and C-reactive

12 protein, a biological marker of inflammatory responses thought to be predictive of increased risk

13 for serious cardiac events.

14

15 **8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies**

16 *Susceptible subpopulations*. Because they lack data on individual subject characteristics,

17 ecologic time series studies provide only limited information on susceptibility factors based on

18 stratified analyses. The relative impact of PM on cardiovascular (and respiratory) admissions

19 reported in ecologic time series studies are generally somewhat higher than those reported for

20 total admissions. This provides some limited support for hypothesizing that acute effects of PM

21 operate via cardiopulmonary pathways or that persons with pre-existing cardiopulmonary disease

22 have greater susceptibility to PM, or both. Although there is some data from the ecologic time

23 series studies showing larger relative impacts of PM on cardiovascular admissions in adults aged

24 $\geq$65 yr as compared with younger populations, the differences are neither striking nor consistent.

25 One recent study reported larger CVD hospitalization effects among persons with current

26 respiratory infections. The individual-level studies of cardiophysiologic function assessed above

27 generally do suggest that elderly persons with pre-existing cardiopulmonary disease are

28 susceptible to subtle changes in heart rate variability in association with PM exposures. Because

29 younger and healthier populations have not yet been assessed, it is not yet possible to say whether

30 the elderly clearly have especially increased susceptibility, but this does represent a reasonable

31 working hypothesis.

1   *Role of other environmental factors*. The ecologic time series studies published since 1996 all

2   have controlled adequately for weather influences. Thus, it is deemed unlikely that residual

3   confounding by weather accounts for the PM associations observed. With one possible

4   exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed

5   extensively as yet in the individual-level studies of cardiac function. Thus, the possibility of

6   confounding in such studies cannot yet be readily discounted. Co-pollutants have been analyzed

7   rather extensively in many of the recent time-series studies of hospital admissions and PM. In

8   some studies, PM clearly carries an independent association after controlling for gaseous co-

9   pollutants. In others, the "PM effects" are markedly reduced once co-pollutants are added to the

10   model; but this may in part be due to colinearity between PM_{10} and co-pollutants and/or the

11   gaseous pollutants such as CO having independent effects on cardiovascular function.

12

13   *Temporal patterns of responses following PM exposure*. The evidence from recent time series

14   studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at lag 0,

15   with some carryover to lag 1, with little evidence for important effects beyond lag 1.

16

17   *Relation of CVD effects to PM size and chemical composition attributes*. Insufficient data

18   exist from the time series CVD admissions literature or from the emerging individual-level

19   studies to provide clear guidance as to which ambient PM components, defined either on the

20   basis of size or composition, determine ambient PM CVD effect potency. The epidemiologic

21   studies published to date have been constrained by the limited availability of multiple PM

22   metrics. Where multiple metrics exist, they often are highly correlated or of differential quality

23   due to differences in numbers of monitoring sites and in monitoring frequency.

24

25   *PM effects on blood characteristics related to CVD events*. Interesting, though limited, new

26   evidence has also been derived which is highly suggestive of associations between ambient PM

27   and increased blood viscosity, increased serum C-reactive protein, and fibrinogen (both related

28   to increased risks of serious cardiac events)

29

30

8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory Hospital Admissions and Medical Visits

8.3.2.1 Introduction

Among the most severe morbidity measures evaluated with regard to PM exposure are hospital admissions. Hospital emergency department (ED) visits represent a related outcome that has also been studied in relation to air pollution. Also doctors' visits represent a related health measure that, although less studied, is relevant to those who also suffer severe health effects. This latter category of pollution-affected persons can represent a large population, yet one largely unevaluated due to the usual lack of centralized data regarding doctors' visits.

This section evaluates present knowledge regarding the epidemiologic associations of ambient PM exposure with respiratory hospital admissions and medical visits. It intercompares various studies examining each of the size-related PM mass exposure measures (e.g., for PM_{10}) and study results for various PM chemical components vis-à-vis their relative associations with health effects, and their respective extents of coherence with PM associations exhibited across related health effects measures. In the following discussion, the main focus for quantitative intercomparisons is on studies and results considering PM metrics that quantitatively measure mass or a specific mass constituent, i.e.,: PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, sulfates ($SO_4^=$), or acidic aerosols (H^+). Study results for other related PM metrics (e.g., Black Smoke; BS) are also considered, but only qualitatively, primarily with respect to their coherence or lack of coherence with studies using mass or composition metrics measured in North America. In order to consider potentially confounding effects of other co-existing pollutants, study results for various PM metrics are presented both for: (1) when the PM metric is the only pollutant in the model; and, (2) the case where a second pollutant (e.g., ozone) is also included. Results from models with more than two pollutants included simultaneously are not used for quantitative estimates of coefficient size or statistical strength, due to increased likelihood of bias and variance inflation due to multi-collinearity of various pollutants (e.g., see Harris, 1975).

The approach taken in this section is: first, to summarize briefly results and implications of the 1996 PM AQCD document regarding this topic; then the most important (pertinent for present purposes) findings from newly available key studies published since the 1996 PM AQCD are discussed in the text. More detailed descriptions of these and other new studies are provided in tabular form in Appendix 8B.

1   Studies of respiratory hospital admissions and medical visits presented in this section were

2   identified by ongoing Medline searches in conjunction with other search strategies. Specific

3   studies were summarized in tables and/or text based on criteria that include the following:

4   (1) preference was given to results reported for PM_{10}, $PM_{10-2.5}$, and $PM_{2.5}$ and/or smaller PM,

5   (2) studies relating respiratory hospital admissions and medical visits to levels of ambient PM

6   exposure in a quantitative manner are the focus of presentation, and (3) other factors discussed

7   earlier in Section 8.1.3 of this chapter.

8

8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996
Particulate Matter Air Quality Criteria Document

11   In the 1996 PM AQCD, it was found that both COPD and pneumonia hospitalization

12   studies showed moderate, but statistically significant, relative risks in the range of 1.06 to

13   1.25 (or 6 to 25% excess risk increment) per 50 $\mu g/m^3$ PM_{10} increase or its equivalent. While a

14   substantial number of hospitalizations for respiratory illnesses occur in those >65 years of age,

15   there are also numerous hospitalizations for those under 65 years of age. Several of the

16   hospitalization studies restricted their analysis by age of the individuals, but did not explicitly

17   examine younger age groups. One exception noted was Pope (1991), who reported an increase in

18   hospitalization for Utah Valley children (aged 0 to 5) for monthly numbers of admissions in

19   relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels

20   used in other studies. Studies examining acute associations between indicators of components of

21   fine particles (e.g., BS; sulfates, $SO_4^=$; and acidic aerosols, H^+) and hospital admissions were also

22   reported as finding significant relationships. While sulfates were especially predictive of

23   respiratory health effects, it was not clear whether the sulfate-related effects were attributable to

24   their acidity, to the broader effects of associated combustion-related fine particles, or to other

25   factors.

26

8.3.2.3 New Respiratory-Related Hospital Admissions Studies

28   New studies since 1996 have confirmed PM associations with respiratory hospital

29   admissions. These studies have examined various admissions categories, including: total

30   respiratory admissions for all ages and by age; asthma for all ages and by age; chronic obstructive

31   pulmonary disease (COPD) admissions (usually for patients > 64 yrs.), and pneumonia

1   admissions (for patients > 64 yrs.). Table 8B-2 in Appendix 8B summarizes important details

2   regarding the study area, study period, study population, PM indices considered and their

3   concentrations, the methods employed, study results and comments, and the "bottom-line" PM

4   index percent excess risks per standard PM increment (e.g., 50 μg/m^3 for PM_{10}) from studies

5   published since the 1996 PM AQCD.

6   The percent excess risk (ER) estimates presented in Table 8B-2 are based upon the relative

7   risks (RR's) provided by the authors, but converted into percent increments per standardized

8   increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies, as

9   discussed in Section 8.1. The ER's shown in the table are for the most positively significant

10 pollutant coefficient. The maximum lag model is used here to provide an estimate of the

11 pollutant-health effects impact.

12   Among the numerous new epidemiological studies published on PM_{10} morbidity, many

13 evaluated effects of relatively high PM_{10} concentrations. However, a large number of studies did

14 evaluate associations at low PM_{10} concentration levels and associations have been reported by

15 several investigators between acute PM_{10} exposures and total respiratory-related hospital

16 admissions for numerous U.S. cities with annual mean ambient concentrations extending to

17 below 50 μg/m^3.

18   The NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} concentrations and hospital

19 admissions by persons 65 and older in 14 U.S. cities is of particular interest. As noted in

20 Table 8-18, this study indicates PM_{10} effects similar to other cities, but with narrower confidence

21 bands, due to its greater power derived by combining multiple cities in the same analysis. This

22 allows significant associations to be identified, despite the fact that many of the cities considered

23 have relatively small populations and that each of the 14 cities had mean PM_{10} below 50 μg/m^3.

24 The cities considered and their respective annual mean/daily maximum PM_{10} concentrations

25 (in μg/m^3) are: Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago

26 (36.4/144.7); Colorado Springs (26.9/147.2); Detroit (36.8/133.6);Minneapolis/St Paul

27 (36.8/133.6); Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3);

28 Provo/Orem (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown

29 (33.1/104.0). As seen in Table 8-18, the PM_{10} association remained even when only those days

30 with PM_{10} less than 50 μg/m^3 were considered. The city-specific value results ranged from -0.06

TABLE 8-18. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-μg/m^3 INCREASE IN PM$_{10}$ IN 14 U.S. CITIES

	CVD		COPD		Pneumonia	
	% Increase	(95% CI)	%Increase	(95% CI)	% Increase	(95% CI)
Constrained lag models (Fixed Effect Estimates)						
One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
PM$_{10}$ <50 μg.m^3 (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Unconstrained distributed Lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.9	(1.46, 2.34)
Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b)

1 for Boulder to 6.43 for Detroit, with a combined result of 9.9 for fixed effects and 8.7 for random

2 effects models for 2 day mean PM$_{10}$ for values less than 50 μg/m^3 for CVD as an example.

3 Janssen et al. (2002) did further analyses for the Samet et al. (2000a,b) 14-city data set

4 examining the associations for the variable prevalence in AC and/or the contribution of different

5 sources to total PM$_{10}$. For COPD and pneumonia, the associations were less significant, but the

6 pattern of association were similar to that for CVD as discussed in Section 8.3.1.

7 If day-to-day increases in air pollution cause rises in hospital admissions, as indicated by

8 time-series studies, then short-term removal of pollution should lower admissions. However, it

9 is rarely possible to test this hypothesis by examining a situation when pollution sources are

10 abruptly "turned off" and then "turned on" again. One past case in point was a steel mill strike

11 and concomitant reductions in both PM and respiratory admissions that were experienced in Utah

12 Valley, but not in surrounding valleys with out the steel mill, as documented by Pope (1991).

13 A more broadly relevant case where this hypothesis was similarly tested was a study of air

14 quality improvements during the Atlanta Summer Olympics of 1996 (Friedman et al., 2001).

15 These improvements were compared to changes that occurred in children's hospital admissions,

16 while weather and other "natural" influences on admissions stayed unchanged from normal.

1   Compared to a baseline period, traffic related pollution declined, with PM_{10} levels declining by

2   16%, and ozone by 28% as a result of the alternative mass transportation strategy implemented to

3   reduce road traffic during the Games. At the same time, SO_2, not related to traffic, actually

4   increased during the Games. Concentrations of both PM and ozone also rose noticeably after the

5   end of the Olympics. A significant reduction in asthma events was associated with ozone

6   concentration, but the PM_{10} association was not statistically significant. While the high

7   correlation between PM and ozone limit the ability to determine which pollutant may have

8   accounted for the reduction in asthma events, this study supports the hypothesis that reductions

9   of acute air pollution levels can provide immediate health improvements.

10   Other U.S. studies finding associations of respiratory-related hospital admissions or

11   medical visits with PM_{10} levels extending below 50 $\mu g/m^3$ include: Schwartz (1995) in Tacoma;

12   Schwartz (1994) in Minneapolis; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999) in

13   Seattle; Gwynn et al. (2000) in Buffalo, NY; Linn et al. (2000) in Los Angeles, Nauenberg and

14   Basu (1999) in Los Angeles; and Moolgavkar et al. (1997) in Minneapolis-St. Paul, MN, but not

15   in Birmingham, AL. The excess risk estimates appear to most consistently fall in the range of

16   5-25% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma visits and hospital admissions

17   usually being higher than those for COPD and pneumonia hospital admissions.

18   Similar associations between increased respiratory related hospital admissions/medical

19   visits and relatively low short-term PM_{10} levels were also reported by various investigators for

20   several non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant

21   associations between PM_{10} (mean = 25.6 $\mu g/m^3$, max. = 131 $\mu g/m^3$) and respiratory admissions in

22   Birmingham, UK; and Atkinson et al. (1999a) found significant increases in hospital admissions

23   for respiratory disease to be associated with PM_{10} (mean = 28.5 $\mu g/m^3$) in London, UK. Hagen

24   et al. (2000) and Prescott et al. (1998) also found positive but non-significant PM_{10} associations

25   with hospital admissions in Drammen, Sweden (mean = 16.8 $\mu g/m^3$) and Edinburgh, Scotland

26   (mean = 20.7 $\mu g/m^3$), respectively. Admissions in Drammen considered relatively small

27   populations, limiting statistical power in this study. Petroeschevsky et al. (2001) examined

28   associations between outdoor air pollution and hospital admissions in Brisbane, Australia during

29   1987-1994 using a light scattering index (BSP) for fine PM. The levels of PM are quite low in

30   this city, relative to most U.S. cities. BSP was positively and significantly associated with total

31   respiratory admissions, but not for asthma.

1 *8.3.2.3.1 Particulate Matter Mass Fractions and Composition Comparisons*

2 While PM_{10} mass is the metric most often employed as the particle pollution index in the

3 U.S. and Canada, some new studies have begun to examine the relative roles of various PM_{10}

4 mass fractions and chemical constituents (such as $SO_4^=$) in the PM-respiratory hospital

5 admissions association. Several new studies report significant associations of increased

6 respiratory-cause medical visits and/or hospital admissions with ambient $PM_{2.5}$ and/or $PM_{10-2.5}$

7 ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit,

8 where all PM metrics (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, H^+) were positively related to pneumonia and COPD

9 admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values

10 generally remaining little changed (but with broader confidence intervals) in multipollutant

11 models including one or more gaseous pollutant (e.g., CO, O_3, NO_2, SO_2). Excess risks for

12 pneumonia admissions in the one pollutant model were 13% (3.7, 22) and 12% (0.8, 24) per

13 25 $\mu g/m^3$ of $PM_{2.5}$ and $PM_{10-2.5}$, respectively; those for COPD admissions were 5.5% (−4.7, 17)

14 and 9.3% (−4.4, 25) per 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$, respectively. Also of note, Moolgavkar

15 found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in

16 Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models; but the

17 magnitudes of the risk estimates dropped by more than half to non-statistically significant levels

18 in two-pollutant models including CO. In the same study, similar magnitudes of excess risk (i.e.,

19 in the range of ca. 4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or

20 $PM_{10-2.5}$ for other age groups (0−19 yr; 20−64 yr) in Los Angeles, as well. Moolgavkar et al.

21 (2000) also found 5.6% (0.2, 11.3) excess risk for all-ages COPD hospital admissions per

22 25 $\mu g/m^3$ $PM_{2.5}$ increase in King County, WA.

23 Tolbert et al. (2000a) reported no significant associations of $PM_{2.5}$ or $PM_{10-2.5}$ with COPD

24 emergency department visits in Atlanta, based on data from less than half of all participating

25 hospitals and ca. 1 yr of supersite air quality data. However, more complete analyses from all

26 participating hospitals over a longer time period are required before this can be adequately

27 evaluated.

28 Gwynn et al. (2000) considered a 2.5 yr period (May 1988-Oct. 1990) in the Buffalo, NY

29 region in a time-series analysis of daily mortality and hospital admissions for total, respiratory,

30 and circulatory hospital admissions categories. Pollutants considered included: PM_{10}, H^+, $SO_4^=$

31 COH, O_3, CO, SO_2, and NO_2. The H^+ and $SO_4^=$ concentrations were determined from daily $PM_{2.5}$

1   samples not analyzed for mass (in order to avoid possible acid neutralization) using the

2   sequential acid aerosol system. Various modeling techniques were applied to control for

3   confounding of effect estimates due to seasonality, weather and day-of-week effects. They found

4   multiple significant pollutant-health effect associations, the most significant being between $SO_4^=$

5   and respiratory hospital admissions. When calculated in terms of increments employed across

6   analyses in this report, various PM RR's were: PM_{10} RR=1.11, 95% C.I.=1.05-1.18(for

7   50 $\mu g/m^3$); H^+ RR=1.06, 95% C.I.=1.03-1.09 (for 75 nmoles/m^3 = 3.6 $\mu g/m^3$, if as H_2SO_4); and

8   $SO_4^=$ RR=1.08, 95% C.I.=1.04-1.12 (for 155 nmoles/m^3=15 $\mu g/m^3$). As in the Burnett et al.

9   (1997a) study described below, H^+ yielded the highest RR per $\mu g/m^3$ of concentration. These

10   various PM metric associations were not significantly affected by inclusion of gaseous

11   co-pollutants in the regression model. Thus, all PM components considered except COH were

12   found to be associated with increased hospital admissions, but H^+, $SO_4^=$ and O_3 had the most

13   coherent associations with respiratory admissions.

14   Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data

15   from hospital admissions for respiratory disease on King County, WA for eight years (1987-94),

16   together with air pollution and weather information. However, their weather controls were

17   relatively crude (i.e., seasonal dummy variables and linear temperature terms). This study is

18   notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$ and for finding

19   significant hospital admission associations only with $PM_{1.0}$. This may suggest that the $PM_{2.5}$ vs.

20   PM_{10} separation may not always be sufficient to differentiate submicron fine particle vs. coarse-

21   particle toxicities.

22   Asthma hospital admission studies conducted in various U.S. communities provide

23   additional important new data. Of particular note is a study by Sheppard et al. (1999) which

24   evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3 and

25   CO) and non-elderly adult (<65 years of age) hospital admissions for asthma in Seattle, WA.

26   PM and CO were found to be jointly associated with asthma admissions. An estimated 4 to 5%

27   increase in the rate of asthma hospital admissions (lagged 1 day) was reported to be associated

28   with interquartile range changes in PM indices (19 $\mu g/m^3$ for PM_{10}, 11.8 $\mu g/m^3$ for $PM_{2.5}$, and

29   9.3 $\mu g/m^3$ for $PM_{10-2.5}$), equivalent to excess risk rates as follows: 13% (95% CI 05, 23) per

30   50 $\mu g/m^3$ for PM_{10}; 9% (95% CI 3, 14) per 25 $\mu g/m^3$ $PM_{2.5}$; 11% (95% CI 3, 20) per 25 $\mu g/m^3$

31   $PM_{10-2.5}$. Also of note for the same region is the Norris et al. (1999) study showing associations

1 of low levels of $PM_{2.5}$ (mean = 12 $\mu g/m^3$) with markedly increased asthma ED, i.e., excess risk =

2 44.5% (CI 21.7, 71.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

3   Burnett et al. (1997a) evaluated the role that the ambient air pollution mix, comprised of

4 gaseous pollutants and PM indexed by various physical and chemical measures, plays in

5 exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases

6 (tracheobronchitis, chronic obstructive long disease, asthma, and pneumonia). They employed

7 daily measures of $PM_{2.5}$ and $PM_{10-2.5}$, aerosol chemistry (sulfates and H^+), and gaseous pollutants

8 (ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide) collected in Toronto, Ontario,

9 Canada, during the summers of 1992, 1993, and 1994. Positive associations were observed for

10 all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most

11 consistently significant pollutant and least sensitive to adjustment for other gaseous and

12 particulate measures. The PM associations with the respiratory hospital admissions were

13 significant for: PM_{10} (RR=1.11for 50 $\mu g/m^3$; CI=1.05-1.17); $PM_{2.5}$ (fine) mass (RR=1.09 for

14 25 $\mu g/m^3$; CI=1.03-1.14); $PM_{10-2.5}$ (coarse) mass (RR=1.13 for 25 $\mu g/m^3$; CI=1.05-1.20); sulfate

15 levels (RR=1.11 for 155 nmoles/m³=15 $\mu g/m^3$; CI=1.06-1.17); and H^+ (RR=1.40 for

16 75 nmoles/m³ = 3.6 $\mu g/m^3$, as H_2SO_4; CI=1.15-1.70). After simultaneous inclusion of ozone in

17 the model, the associations with the respiratory hospital admissions remained significant for:

18 PM_{10} (RR=1.10; CI=1.04-1.16); fine mass (RR=1.06; CI=1.01-1.12); coarse mass (RR=1.11;

19 CI=1.04-1.19); sulfate levels (RR=1.06; CI=1.0-1.12); and H^+ (RR=1.25; CI=1.03-1.53), using

20 the same increments. Of the PM metrics considered here, H^+ yielded the highest RR estimate.

21 Regression models that included all recorded pollutants simultaneously (with high

22 intercorrelations among the pollutants) were also presented.

23   There have also been numerous new time-series studies examining associations between air

24 pollution and respiratory-related hospital admissions in Europe, as summarized in Appendix 8B,

25 Table 8B-2, but most of these studies relied primarily on black smoke (BS) as their PM metric.

26 BS is a particle reflectance measure that provides an indicator of particulate blackness and is

27 highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton, 1982).

28 In the U.S., Coefficient of Haze (COH) is a metric of particle transmittance that similarly most

29 directly represents a metric of particle blackness and ambient elemental carbon concentration

30 (Wolff et al., 1983) and has been found to be highly correlated with BS (r = 0.9) (Lee et al.,

31 1972). However, the relationship between airborne carbon and total mass of overall aerosol

1   (PM) composition varies over time and from locality to locality, so the BS-mass ratio is less

2   reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-

3   mass relationship is likely to be very different between Europe and the U.S., largely due to

4   differences in local PM source characteristics (e.g., percentages of diesel powered motor

5   vehicles). Therefore, while these European BS-health effects studies are of qualitative use for

6   evaluating the PM-health effects associations, they are not as useful for quantitative assessment

7   of PM effects relevant to the U.S.

8   Hagan et al. (2000) compared the association of PM_{10} and co-pollutants with hospital

9   admissions for respiratory causes in Drammen, Norway during 1994-1997. Respiratory

10 admissions averaged only 2.2 per day; so, the power of this analysis is weaker than studies

11 looking at larger populations and longer time periods. The HEI I.B Multi-city Report modeling

12 approach was employed. While a significant association was found for PM_{10} as a single

13 pollutant, it became non-significant in multiple pollutant models. In two pollutant models, the

14 associations and effect size of pollutants were generally diminished, and when all eight pollutants

15 were considered in the model, all pollutants became non-significant. These results are typical of

16 the problems of analyzing and interpreting the coefficients of multiple pollutant models when the

17 pollutants are even moderately inter-correlated over time. A unique aspect of this work was that

18 benzene was considered in this community strongly affected by traffic pollution. In two pollutant

19 models, benzene was most consistently still associated. The authors conclude that PM is mainly

20 an indicator of air pollution in this city and that emissions from vehicles seem most important for

21 health effects. Thompson et al. (2001) report a similar result in Belfast, Northern Ireland, where,

22 after adjusting for multiple pollutants, only the benzene level was independently associated with

23 asthma emergency department admissions.

24   The most recent European air pollution health effects analyses have mainly been conducted

25 as part of the APHEA study, which evaluated 15 European cities from 10 different countries with

26 a total population of over 25 million. All studies used a standardized data collection and analysis

27 approach, which included consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2,

28 and O_3) and the use of time-series regression addressing: seasonal and other long-term patterns;

29 influenza epidemics; day of the week; holidays; weather; and autocorrelation (Katsouyanni et al.,

30 1996). The general coherence of the APHEA results with other results gained under different

31 conditions strengthens the argument for causality in the air pollution-health effects association.

1   In earlier studies, the general use of the less comparable suspended particle (SPM) measures and

2   BS as PM indicators in some of the APHEA locations and analyses lessens the quantitative

3   usefulness of such analyses in evaluating associations between PM and health effects most

4   pertinent to the U.S. situation. However, Atkinson et al. (2001) report results of PM_{10} analysis in

5   a study of eight APHEA cities.

6

7   *8.3.2.3.2 Methodological Studies*

8   One study by Lumley and Sheppard (2000) applied a simulation approach to examine the

9   effects of seasonal confounding and model selection on hospital admissions effect estimates in

10   Seattle, Washington. It was found that the bias introduced by model selection was small, but

11   could be on the same order as the estimated health impacts. This problem was the case when

12   seasonal adjustments were not accounted for in the model, and was larger when the maximum

13   lag of many was selected. However, the distributed lag nature of air pollution effects was not

14   simulated, making the tests of the maximum lag vs. real effect unrealistic. Also, in the now usual

15   case in which seasonal adjustments were included, any bias was consistently much smaller and

16   was non-significant in cases where there was no simulated PM effect. This suggests that model

17   selection bias is not a concern in the type of modeling routinely done today, and also points out

18   the need to consider statistical significance when evaluating and inter-comparing effect estimates.

19   Several studies looked at the potential influence of exposure error on pollutant impact

20   estimates. Lipfert (2000) surveyed the sources and magnitudes of such errors and concluded that

21   they can have "profound effects on the results of epidemiological studies", noting especially

22   comparisons between fine particles and less accurately measured coarse particle associations

23   with health. In a related paper, Lipfert and Wyzga (1999) consider this issue and argue against

24   the use of statistical significance for pollutant impact inter-comparisons because the distribution

25   characteristics of the variable can play a role in its strength of association. They recommend the

26   use of effect size to inter-compare pollutants, even though differing choices of a particular

27   increment for the pollutant effect estimation (e.g., IQR vs. mean vs. median vs. max-mean, etc.)

28   will usually give differing rankings across pollutants, as their relative sizes are influenced by

29   pollutant distribution, as well. The authors argue that, until uncertainties have been fully

30   explored, such as those introduced by exposure error, such epidemiological studies should only

31   be considered as suggestive of causality. Huang and Batterman (2000) also look at exposure

1   error, noting that most studies have not looked at the population exposure errors, and concluding

2   that, "Unless exposure levels among groups are verified, it cannot be determined whether

3   nonsignificant associations between exposure and health endpoints indicate a lack of measurable

4   health effects, or are merely a result of exposure misclassification". However, a recent study by

5   Sheppard and Damian (2000) using quasi-likelihood simulation techniques investigated the effect

6   of pure measurement error, but not spatial or within-day personal exposure variations,

7   concluding that adjustment for measurement error does not alter the conclusions from the time

8   series analyses typically reported in the literature.

9   Schwartz (2001) examined another relevant methodological and mechanistic aspect of the

10   PM-health association: the harvesting question (i.e., as to whether the associations between air

11   pollution and health effects are due to the moving up of an event [e.g., death] that would have

12   happened in a few days, anyway, or not)? Using a smoothing technique, he estimated the "net"

13   change in mortality and hospital admissions in Chicago associated with PM, after accounting for

14   any decline in events in the follow-up period, ranging from 15 to 60 days. Analyses indicated

15   that the health effect estimates stayed the same, or increased, when any harvesting effects were

16   adjusted for in the analysis. He concluded that the results are consistent with air pollution

17   increasing the size of the risk pool, and for most of the air pollution associated deaths being

18   advanced by months to years.

19   Dewanji and Moolgavkar (2000) implemented a flexible parametric model analysis in the

20   example of multiple hospital admissions for chronic respiratory disease in King County, WA,

21   that views the data on each subject as the realization of a point process, which allows

22   incorporation of subject specific covariate and the previous history of the process. In single

23   pollutant analyses, measures of PM (PM_{10} and $PM_{2.5}$) and CO are associated with hospital

24   admissions. The effect of PM was stronger than that of CO in the multipollutant models. This

25   result is inconsistent with other analysis of the same data (Moolgavkar et al., 2000) which find

26   that the effect of PM becomes insignificant when CO is simultaneously considered in the

27   analysis.

28   Pollen is an atmospheric constituent that might potentially be a factor that may confound

29   PM-asthma admissions associations, if it is correlated with both PM and hospital admissions.

30   In a London study, airborne pollen did not confound the analysis of air pollution (including black

31   smoke) and daily admissions for asthma during the time period 1987-1992 (Anderson et al.,

1   1998). Moolgavkar et al. (2000) in a study in Seattle found that adding pollens to PM time-series

2   regressions of respiratory admissions diminished the PM effect estimates more for PM_{10} than that

3   for $PM_{2.5}$. Confounding by pollens would require correlation between daily $PM_{2.5}$ levels and

4   seasonal pollution events and weather-related specification events. Further, for a different

5   outcome measure, Delfino et al. (1996) found that pollen was not associated with asthma

6   symptoms in an asthma panel (see Section 8.3.3)

7

8   **8.3.2.4 Key New Respiratory Medical Visits Studies**

9   As discussed above, medical visits include both hospital emergency department (ED) visits

10   and doctors' office visits. As in the past PM AQCD's, most of the available morbidity studies

11   presented in Appendix 8B, Table 8B-3 are of ED visits and their associations with air pollution.

12   These studies collectively confirm the results provided in the previous AQCD, indicating a

13   positive and significant association between ambient PM levels and increased respiratory-related

14   hospital visits.

15   Of the medical visit and hospital admissions studies since the 1996 PM AQCD, the most

16   informative are those that evaluate health effects associations at levels below previously well-

17   implicated PM concentrations. In the case of medical visits, the Norris et al. (1999, 2000) studies

18   of asthma ED visits found significant PM-associated health effects among children in Seattle,

19   even at quite low average PM levels and even after incorporating the effects of other air

20   pollutants (study mean $PM_{10} = 21.7$ $\mu g/m^3$; estimated mean $PM_{2.5} = 12$ $\mu g/m^3$). Tolbert et al.

21   (2000b) reported a significant PM_{10} association with pediatric ED visits in Atlanta where the

22   maximum PM_{10} concentration was 105 $\mu g/m^3$. The Lipsett et al. (1997) study of winter air

23   pollution and asthma emergency visits in Santa Clara County, CA, may provide insight where

24   one of the principal sources of PM_{10} is residential wood combustion (RWC). Their results

25   demonstrate an association between PM and asthma concentrations. Also, Delfino et al. (1997)

26   found significant PM_{10} and $PM_{2.5}$ associations for respiratory ED visits among older adults in

27   Montreal when mean $PM_{10} = 21.7$ $\mu g/m^3$ and mean $PM_{2.5} = 12.2$ $\mu g/m^3$. Medina et al. (1997)

28   reported significant associations between doctor's asthma house visits and PM_{13} (which would

29   have a slightly higher concentration value than PM_{10}) in Paris when mean $PM_{13} = 25$ $\mu g/m^3$ and

30   maximum daily $PM_{13} = 95$ $\mu g/m^3$. Hajat et al. (1999) reported significant PM_{10} associations with

31   asthma doctor's visits for children and young adults in London when mean $PM_{10} = 28.2$ $\mu g/m^3$

1   and the PM_{10} 90th percentile was only 46.4 $\mu g/m^3$. Overall, then, numerous new medical visits

2   studies indicate PM-health effects associations at lower $PM_{2.5}$ and PM_{10} levels than demonstrated

3   previously for this health outcome.

4

5   *8.3.2.4.1 Scope of Medical Visit Morbidity Effects*

6   Several of these recent medical visit studies consider a new endpoint for comparison with

7   ED visits: visits in the primary care setting. In particular, key studies showing PM-health effects

8   associations for this health outcome include: the study by Medina et al. (1997) for Paris, France

9   which evaluated doctors' visits to patients in that city; the study by Hajat et al. (1999) that

10   evaluated the relationship between daily General Practice (GP) doctor consultations for asthma

11   and other lower respiratory disease (LRD) and air pollution in London, UK; the study by

12   Choudhury et al. (1997) of private asthma medical visits in Anchorage, Alaska; and the study by

13   Ostro et al. (1999b) of daily visits by young children to primary care health clinics in Santiago,

14   Chile for upper or lower respiratory symptoms.

15   While limited in number, the above studies collectively provide new insight into the fact

16   that there is a broader scope of severe morbidity associated with PM air pollution exposure than

17   previously documented. As the authors of the London study note: "There is less information

18   about the effects of air pollution in general practice consultations but, if they do exist, the public

19   health impact could be considerable because of their large numbers." Indeed, the studies of Paris

20   doctors' house calls and London doctors' GP office visits both indicate that the effects of air

21   pollution, including PM, can affect many more people than indicated by hospital admissions

22   alone.

23   These new studies also provide indications as to the quantitative nature of medical visits

24   effects, relative to those for hospital admissions. In the London case, comparing the number of

25   admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the

26   1999 study (Hajat et al., 1999) indicates that there are approximately 24 asthma GP visits for

27   every asthma hospital admission in that city. Also, comparing the PM_{10} coefficients indicates

28   that the all-ages asthma effect size for the GP visits (although not statistically different) was

29   about 30% larger than that for hospital admissions. Similarly, the number of doctors' house calls

30   for asthma approximated 45/day in Paris (based on an average 9 asthma house calls in the SOS-

31   Medocina data base, representing 20% of the total; Medina et al., [1997]), versus an average

1   14 asthma admissions/day (Dab et al., 1996), or a factor of 3 more doctors' house calls than

2   hospital admissions. Moreover, the RR for Paris asthma doctors' house calls was much higher

3   than asthma admissions (RR=1.18 for 25 μg/m^3 BS for house calls vs. RR=1.01 per 25 μg/m^3 BS

4   for hospital admissions). Thus, these new studies suggest that looking at only hospital

5   admissions and emergency hospital visit effects may greatly underestimate the overall numbers

6   of respiratory morbidity events in a population due to acute ambient PM exposure.

7

8   *8.3.2.4.2 Evaluation of Factors Potentially Affecting Respiratory Medical Visit*
9   *Study Outcomes*

10   Some newly available studies have examined certain factors that might extraneously affect

11   the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias

12   and random variability in diagnostic classification of air pollution and daily cardiac respiratory

13   emergency department visits such as asthma, COPD, respiratory infection and cardiac. They

14   concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels.

15   Also, Stieb et al. (1998b) reported that for a population of adults visiting an emergency

16   department with cardiac respiratory disease, fixed site sulfate monitors appear to accurately

17   reflect daily variability in average personal exposure to particulate sulfate, whereas particulate

18   acid exposure was not as well represented by fixed site monitors. Another study investigated

19   possible confounding of respiratory visit effects due to pollens. In London, Atkinson et al.

20   (1999a) studied the association between the number of daily visits to emergency departments for

21   respiratory complaints and measures of outdoor air pollution for PM_{10}, NO_2, SO_2 and CO. They

22   examined different age groups and reported the strongest association for children for visits for

23   asthma, but were unable to separate the effects of PM_{10} and SO_2. Pollen levels did not influence

24   the results, similar to results from the asthma panel studies described below in Section 8.3.3.

25

26   **8.3.2.5 Identification of Potential Susceptible Subpopulations**

27   Associations between ambient PM measures and respiratory admissions have been found

28   for all age groups, but older adults and children have been indicated by a number of hospital

29   admissions studies to exhibit the most consistent PM-health effects associations in the literature.

30   As reported in this and previous PM AQCDs, numerous studies of older adults (e.g., those 65+

31   years of age) have related acute PM exposure with an increased incidence of hospital admissions

1   (e.g., see Anderson et al, 1998). However, only a limited number have specifically studied

2   children as a subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital

3   admissions associations as a function of age in the province of Ontario, reporting that the largest

4   percentage increase in admissions was found among infants (neonatal and post-neonatal, one year

5   or less in age).

6   Considerable efforts have aimed at identifying and quantifying air pollution effects among

7   potentially especially susceptible sub-populations of the general public, especially among

8   children. Burnett et al. (2001b) studied the association between air pollution and hospitalization

9   for acute respiratory diseases in children less than 2 years of age in Toronto, Canada during

10   1980-1994. In single pollutant analyses, $PM_{2.5}$, $PM_{10-2.5}$, ozone, NO_2, and CO were all significant

11   predictors of young children's respiratory admissions, but only ozone and CO stayed significant

12   in 2 pollutant models, with ozone also having a robust effect estimate in co-pollutant models.

13   These effects were found to be bigger than those for older children or adults studied in a previous

14   publication (Burnett et al., 1994). Two other recent studies of children's morbidity support the

15   indication of air pollution effects among children. Pless-Mulloli et al. (2000) looked at

16   children's respiratory health and air pollution near opencast coal mining sites in a cohort of

17   nearly 5,000 children aged 1-11 in England. Mean levels were not high (mean less than

18   20 $\mu g/m^3$ PM_{10}), but statistically significant PM_{10} associations were found with respiratory

19   symptoms. A roughly 5 percent increase General Practitioner medical visits was also noted, but

20   the effect was not significant in this cohort. Ilabaca et al. (1999) found an association between

21   levels of fine PM and emergency visits for pneumonia and other respiratory illnesses among

22   children less than 15 years of age living in the eastern part of Santiago, Chile, where the levels of

23   $PM_{2.5}$ were very high (mean=71.3 $\mu g/m^3$) during 1995-1996. The authors found it difficult to

24   separate out the effects of various pollutants, but concluded that PM (especially the fine

25   component) is associated with the risk of these respiratory illnesses. Overall, these new studies

26   support past assertions that children, and especially those less than 2 years of age, are especially

27   susceptible to the adverse health effects of air pollution.

28   Several new studies have further investigated the hypothesis that the elderly are especially

29   affected by air pollution. Zanobetti et al. (2000b) analyzed Medicare hospital admissions for

30   heart disease, COPD, and pneumonia in Chicago, IL between 1985 and 1994, finding that the

31   PM_{10} risk estimate was nearly doubled by the co-presence of respiratory infections, but that there

1   was no effect modification by sex or race. Zanobetti et al. (2000a) similarly examined PM_{10}

2   associations with hospital admissions for heart and lung disease in ten U.S. cities, finding an

3   overall association for COPD, pneumonia, and CVD. They found that these results were not

4   significantly modified by poverty rate or minority status in this population of Medicare patients.

5   Ye et al. (2001) examined emergency transports to the hospital. Both PM_{10} and NO_2 levels were

6   significantly associated with daily hospital transports for angina, cardiac insufficiency,

7   myocardial infarction, acute and chronic bronchitis, and pneumonia. The pollutant effect sizes

8   were generally found to be greater in men than in women, except those for angina and acute

9   bronchitis, which were the same across genders. Thus, in these various studies, cardiopulmonary

10   hospital visits and admissions among the elderly were seen to be consistently associated with PM

11   levels across numerous locales in the U.S. and abroad, generally without regard to race or

12   income; but sex was sometimes an effect modifier.

13   Gwynn and Thurston (2001) examined race as a factor in the air pollution-hospital

14   admissions association. This study considered persons of all ages in New York City during

15   1988-1990, which provided a large and diverse population ideal for investigating this question.

16   Although not statistically different from each other, the various air pollutants' relative risk

17   estimates for the Hispanic non-White category in NYC were generally larger in magnitude than

18   those of the non-Hispanic White group. The greatest difference between the White and non-

19   White subgroups was observed for O_3, but the same trend was found for PM_{10} and sulfates.

20   However, when insurance status was used as an indicator of socioeconomic/health coverage

21   status, higher RR's were indicated for the poor and working poor (i.e., those on Medicaid and the

22   uninsured) than for economically better off (i.e., the privately insured), even among the non-

23   Hispanic Whites. This result is consistent with the past analyses in California by Nauenberg and

24   Basu (1999). Thus, the within-race analyses by insurance coverage suggested that most of the

25   generally higher effects of air pollution found for minorities (i.e., Hispanics and non-Whites)

26   were actually caused by overall socioeconomic and/or health care disparities in these populations

27   vs. the generally wealthier non-Hispanic White population. This suggests that those living in

28   poverty may represent an especially affected sub-population.

29   The respiratory-related hospital admissions studies summarized in Appendix 8B, Table

30   8B-2 reveals that the PM RR's for all children (e.g., 0-18) are not usually noticeably larger than

31   those for adults, but such comparisons of RR's must adjust for differences in the baseline risks

1   for each group. For example, if hospital admissions per 100,000 per day for young children are

2   double the rate for adults, then they will have a pollution relative risk (RR) per $\mu g/m^3$ that is half

3   that of the adults given the exact same impact on admissions/100,000/$\mu g/m^3$/day. Thus, it is

4   important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this

5   information is usually not available (especially regarding the population catchment for each age

6   group in each study).

7   One of the few indications that is notable when comparing children with other age group

8   effect estimates in Table 8B-2 is the higher excess risk estimate for infants (i.e., the group <1 yr.

9   of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate

10 roughly twice as large as for other children or adults. This is confirmatory of the excess risk

11 pattern previously found in the above-noted Burnett et al. (1994) study for respiratory-related

12 hospital admissions.

13

14 **8.3.2.6 Summary of Key Findings on Acute Particulate Matter Exposure and**
15 **Respiratory-Related Hospital Admissions and Medical Visits**

16   The results of new studies discussed above are generally consistent with and supportive of

17 findings presented in the previous PM AQCD (U.S. Environmental Protection Agency, 1996a),

18 with regard to ambient PM associations of short-term exposures with respiratory-related hospital

19 admissions/medical visits. Excess risk estimates for specific subcategories of respiratory-related

20 hospital admissions/medical visits for U.S. cities are summarized in Tables 8-19 to 8-22 and

21 graphically depicted in Figure 8-13. The excess risk estimates fall most consistently in the range

22 of 5 to 25% per 50 $\mu g/m^3$ PM_{10} increments, with those for asthma visits and hospital admissions

23 tending to be somewhat higher than for COPD and pneumonia hospital admissions.

24   More limited new evidence substantiates increased risk of respiratory-related hospital

25 admissions due to ambient fine particles ($PM_{2.5}$, $PM_{1.0}$, etc.) and also points towards such

26 admissions being associated with ambient coarse particles ($PM_{10-2.5}$). Excess risk estimates tend

27 to fall in the range of ca. 5.0 to 15.0% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ for overall respiratory

28 admissions or for COPD admissions, whereas larger estimates are found for asthma admissions

29 (ranging upwards to ca. 40 to 50% for children < 18 yr. old in one study).

30   Various new medical visits studies (including non-hospital physician visits) indicate that

31 the use of hospital admissions alone can greatly understate the total clinical morbidity effects of

TABLE 8-19. SUMMARY OF UNITED STATES PM$_{10}$ RESPIRATORY HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels $\mu g/m^3$	Co-Pollutants Measured	Lag	Effect Estimate (95% CL)
Moolgavkar et al. (1997) Minneapolis, St. Paul (MSP Birmingham (BI) BI	Respiratory Respiratory Respiratory Respiratory	MSP PM$_{10}$ 34 MSP PM$_{10}$ 34 BI PM$_{10}$ 43.4 BI PM$_{10}$ 43.4	— O$_3$ — O$_3$	1 1 0 0	8.7 (4.6, 13) 6.9 (2.7, 11.3) 1.5 (−1.5, 4.6) 3.2 (−0.7, 7.2)
Gwynn et al. (2000)	Respiratory	PM$_{10}$ mn/max 24.1/90.8	gaseous pollutants	0	11% (4.0, 18)
Linn et al. (2000)	Respiratory	45.5	CO, NO$_2$, O$_3$	0	3.3 (1.7, 5)
Schwartz et al. (1996b)	Respiratory	43	SO$_3$	—	5.8 (0.5, 11.4)
Zanobetti and Schwartz (2001)	Respiratory COPD	PM$_{10}$ - 33 med	—	—	w/ diabetes: 2.29 (−0.76, 5.44) w/o diabetes: 1.50 (0.42, 2.6)
Samet et al. (2000a,b)	COPD	PM$_{10}$ - 32.9	SO$_2$, O$_3$, NO$_2$, CO	0 1	7.4 (5.1, 9.8) 7.5 (5.3, 9.8)
Zanobetti et al. (2000a)	COPD	PM$_{10}$ - 32.9	SO$_2$, O$_3$, CO	0-1	10.6 (7.9, 13.4)
Chen et al. (2000)	COPD	PM$_{10}$ - 36.5	—	—	9.4 (2.2, 17.1)
Zanobetti et al. (2000b)	COPD	33.6	—	0	w/o prior RI: 8.8 (3.3, 14.6) w/ prior RI: 17.1 (−6.7, 46.9)
Lippman et al. (2000)	COPD	PM$_{10}$ - 31	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	3 3	No Co Poll: 9.6 (−5.1, 27) Co Poll: 1.0 (−15, 20)
Moolgavkar et al. (2000)	COPD	PM$_{10}$ - 30.0	none CO	2 2	No Co-Poll: 5.1 (0, 10.4) Co-Poll: 2.5 (−2.5, 7.8)
Moolgavkar (2000a)	COPD (>64 yrs) (median)	PM$_{10}$ - 35, Chicago PM$_{10}$ -44, LA PM$_{10}$ - 41, Phoenix PM$_{10}$ - 44, LA	— — — CO	0 2 0 2	2% (−0.2, 4.3) 6.1 (1.1, 11.3) 6.9 (−4.1, 19.3) 0.6 (−5.1 6.7) Two pollutant model
Samet et al. (2000a,b)	Pneumonia	PM$_{10}$ - 32.9	SO$_2$, O$_3$, NO$_2$, CO	0 1	8.1 (6.5, 9.7) 6.7 (5.3, 8.2)
Zanobetti et al. (2000b)	Pneumonia	33.6	—	0	w/o prior asthma: 11 (7.7, 14.3) w/o prior asthma: 22.8 (5.1, 43.6)
Lippman et al. (2000)	Pneumonia	PM$_{10}$ - 31	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	1 1	No Co Poll: 22 (8.3, 36) Co Poll: 24 (8.2, 43)
Zanobetti et al. (2000a)	Pneumonia	PM$_{10}$ - 32.9	SO$_2$, O$_3$, CO	0-1	8.1 (6.5, 9.7)
Jacobs et al. (1997)	Asthma	34.3	O$_3$, CO	—	6.11 (NR)
Sheppard et al. (1999)	Asthma	PM$_{10}$ - 31.5	CO, O$_3$, SO$_2$	1	13.7 (5.5, 22.6)
Nauenberg and Basu (1999)	Asthma	44.81	O$_3$	0	16.2 (2.0, 3.0)

TABLE 8-20. SUMMARY OF UNITED STATES PM$_{2.5}$ RESPIRATORY HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels $\mu g/m^3$	Two-Pollutants Co-Pollutants	Lag	Effect Estimate (95% CL)
Lumley and Heagerty (1999)	Respiratory	PM$_1$, NR	none	1	5.9 (1.1, 11.0)
Lippmann et al. (2000)	COPD	PM$_{2.5}$ - 18	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	3 3	No Poll: 5.5 ($-$4.7, 17) Co Poll: 2.8 ($-$9.2, 16)
Moolgavkar et al. (2000)	COPD	PM$_{2.5}$ - 18.1	none CO	3 3	6.4 (0.9, 12.1) 5.6 (0.2, 11.3)
Moolgavkar (2000a)	COPD (>64 yrs) (median)	PM$_{2.5}$ - 22, LA	—	2	5.1 (0.9, 9.4)
		PM$_{2.5}$ - 22, LA	CO	2	2.0 ($-$2.9, 7.1) Two pollutant model
Lippmann et al. (2000)	Pneumonia	PM$_{2.5}$ - 18	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	1 1	No Poll: 13 (3.7, 22) Co Poll: 12 (1.7, 23)
Sheppard et al. (1999)	Asthma	PM$_{2.5}$ - 16.7	CO, O$_3$, SO$_2$	1	8.7 (3.3, 14.3)
Freidman et al. (2001)	Asthma	PM$_{2.5}$ (36.7 - 30.8 decrease)	O$_3$	3 d. cu m	1.4 (0.80-2.48)

TABLE 8-21. SUMMARY OF UNITED STATES PM$_{10-2.5}$ RESPIRATORY HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels $\mu g/m^3$	Two-Pollutant Co-Pollutants	Lag	Effect Estimates (95% CL)
Moolgavkar (2000a)	COPD	PM$_{10-2.5}$	—	3	5.1% (-0.4, 10.9)
Lippmann et al. (2000)	COPD	PM$_{10-2.5}$ -12	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	3 3	No Poll: 9.3 ($-$4.4, 25) Co Poll: 0.3 ($-$14, 18)
	Pneumonia	PM$_{10-2.5}$ -12	SO$_2$, O$_3$, NO$_2$, CO, H$^+$	3 3	No Poll: 9.3 ($-$4.4, 25) Co Poll: 0.3 ($-$14, 18)
Sheppard et al. (1999)	Asthma	PM$_{10-2.5}$ - 16.2	CO, O$_3$, SO$_2$	1	11.1 (2.8, 20.1)

1   air pollution. Thus, these results support the hypothesis that considering only hospital

2   admissions and emergency hospital visit effects may greatly underestimate the numbers of

3   medical visits occurring in a population as a result of acute ambient PM exposure. Those groups

4   identified in these morbidity studies as most strongly affected by PM air pollution are older

5   adults and the very young.

TABLE 8-22. SUMMARY OF UNITED STATES PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ ASTHMA MEDICAL VISIT STUDIES*

Reference	Outcome Measures	Mean Levels (μg/m^3)	Co-Pollutants Measured	Lag	Effect Estimate (95% CL)
PM$_{10}$					
Choudhury et al. (1997)	Asthma	PM$_{10}$ - 41.5	Not considered	0	20.9 (11.8, 30.8)
Lipsett et al. (1997)	Asthma	PM$_{10}$ - 61.2	NO$_2$, O$_3$	2	34.7 (16, 56.5) at 20 °C
Norris et al. (1999)	Asthma	PM$_{10}$ - 21.7	CO, SO$_2$, NO$_2$	1	SP 75.9 (25.1, 147.4)
		PM$_{10}$		1	MP 75.9 (16.3, 166)
Norris et al. (2000)	Asthma	PM$_{10}$ - Spokane 27.9	MP	3	2.4 (−10.9, 17.6)
		PM$_{10}$ - Seattle 21.5	MP	3	56.2 (10.4, 121.1)
Tolbert et al. (2000b)	Asthma	PM$_{10}$ - 38.9	O$_3$	1	SP 13.2 (1.2, 26.7)
				1	MP 8.2 (−7.1, 26.1)
Tolbert et al. (2000a)	Asthma	PM$_{10}$ - 29.1	NO$_2$, O$_3$, CO, SO$_2$	0-2	18.8 (−8.7, 54.4)
PM$_{2.5}$					
Norris et al. (1995)	Asthma	PM$_{2.5}$ - 12.0	CO, SO$_2$, NO$_2$	1	SP 44.5 (21.7, 71.4)
				1	MP 51.2 (23.4, 85.2)
Tolbert et al. (2000a)	Asthma	PM$_{2.5}$ - 19.4	NO$_2$, O$_3$, CO, SO$_2$	0-2	2.3 (−14.8, 22.7)
PM$_{10-2.5}$					
Tolbert et al. (2000a)	Asthma	PM$_{10-2.5}$ - 9.39	NO$_2$, O$_3$, CO, SO$_2$	0-2	21.1 (−18.2, 79.3)

*SP = single pollutant model; MP = multipollutant model.
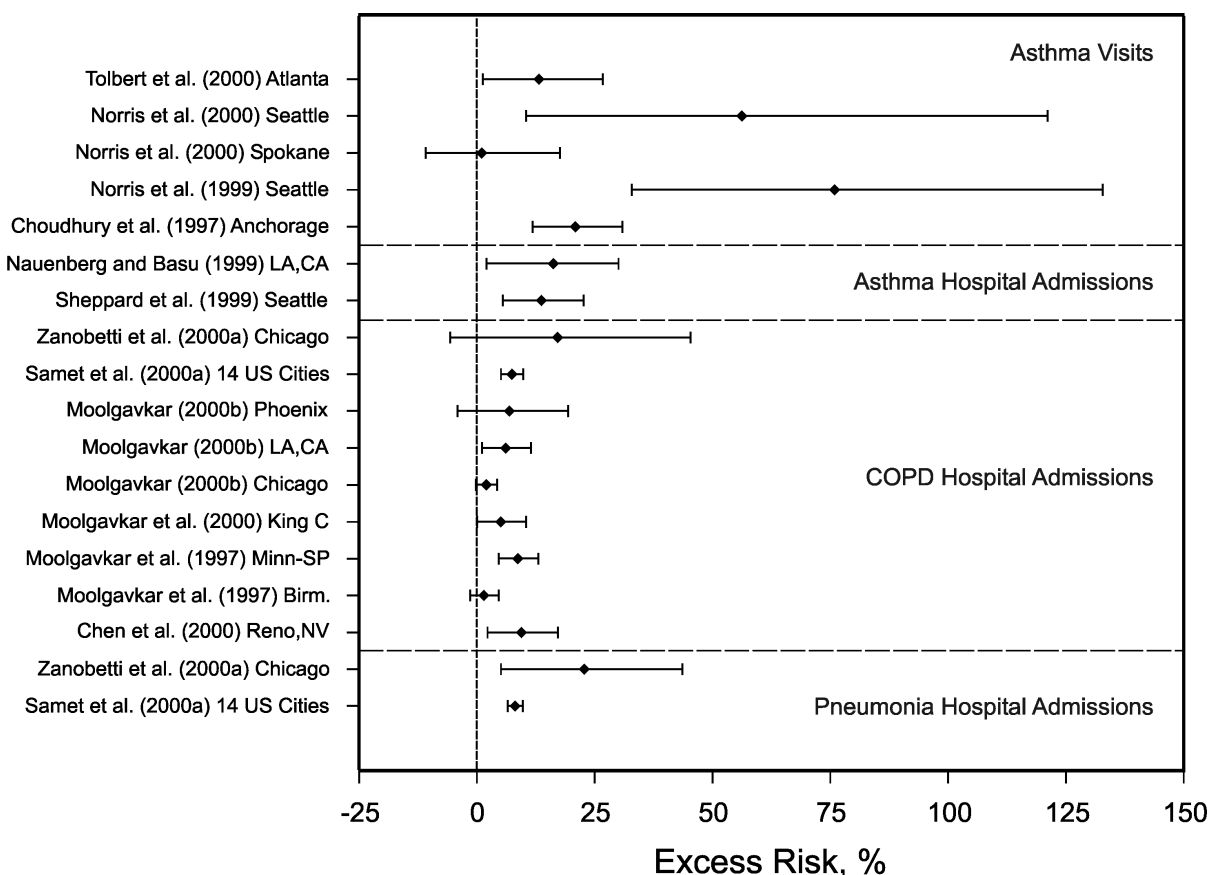
Figure 8-13. **Maximum excess risk of respiratory-related hospital admissions and visits per 50-μg/m^3 PM$_{10}$ increment in selected studies of U.S. cities.**

8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory disease studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to PM$_{10}$. The models for analysis varied and the populations included several different subgroups. Pulmonary function studies were suggestive of short term effects resulting from ambient PM exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min resulting from an increase of 50 μg/m^3 in 24-h PM$_{10}$ or its equivalent, with somewhat larger effects in symptomatic groups such as asthmatics. Studies using FEV$_1$ or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies were less numerous than the acute studies, and the results were inconclusive.

8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms

The available acute respiratory symptom studies discussed in the 1996 PM AQCD included several different endpoints, but typically presented results for: (1) upper respiratory symptoms, (2) lower respiratory symptoms, or (3) cough. These respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

The earlier studies of morbidity health outcomes of PM_{10} exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) studied respiratory symptoms in two panels of asthmatics in the Utah Valley. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness (LRI) and the second panel of 21 subjects aged 8 to 72 for LRI of 1.01 (0.81, 1.27) for exposure to PM_{10}. Ostro et al. (1991) reported no association for $PM_{2.5}$ exposure in a panel of 207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 in central Los Angeles, reported a relationship of shortness of breath to O_3 and PM_{10}, but could not separate effects of the two pollutants (Ostro et al., 1995). These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Numerous new studies of short-term PM exposure effects on lung function and respiratory symptoms published since 1996 were identified by an ongoing medline search.. Most of these followed a panel of subjects over one or more periods and evaluated daily lung function and/or respiratory symptom associations with changes in ambient PM_{10}, $PM_{10-2.5}$, and/or $PM_{2.5}$. Lung function was usually measured daily with many studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF). Most analyses included both morning and afternoon measurements. A variety of respiratory symptoms were measured, including cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Finally, several measures of airborne particles were used, including: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, ultrafine PM, TSP, BS, and sulfate fraction of ambient PM.

These various studies are summarized in several tables presented in Appendix 8B. Data on physical and chemical aspects of ambient PM levels (especially for PM_{10}, $PM_{10-2.5}$. $PM_{2.5}$, and

1	smaller size fractions) are of particular interest, as are new studies examining health outcome
2	effects and/or exposure measures not studied as much in the past. Each table is organized by
3	study location, PM measure, etc. Where possible, results are presented in terms of the units
4	described earlier. Specific studies were selected for summarization based on the following
5	criteria:

6   • Peak flow was used as the primary lung function measurement of interest.

7   • Cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as
8   measures of respiratory symptoms when available.

9   • Quantitative relationships were estimated using PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and/or smaller PM
10   as independent variables.

11   • The analysis of the study was done such that each individual served as their own control.

12   Other factors are discussed earlier in Section 8.1.3 of this chapter selection of Studies for

13   Review, as well as in Chapter 1.

14

15   *8.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects*

16   Tables 8B-4 and 8B-5 in Appendix B summarize short-term PM exposure effects on lung

17   function and respiratory symptoms, respectively, in asthmatic subjects. The peak flow analyses

18   results for asthmatics tend to show small decrements for PM_{10} and $PM_{2.5}$ as shown in studies to

19   include Gielen et al. (1997), Peters et al. (1997b), Romieu et al. (1997), and Pekkanen et al.

20   (1997) listed in summary Table 8-23 for PM_{10}, and Table 8-24 for $PM_{2.5}$, and in more detail in

21   Appendix 8B, Table 8B-4. Pekkanen et al. (1997) reported similar changes in peak flow to be

22   related to several sizes of PM with PN 0.032-0.10 -0.970 (0.502) $l(cm^3)$ and $PM_{1.0-3.2}$ -0.901

23   (0.536) and PM_{10} -1.13 (0.478) for morning PEF lag 2. Peters et al. (1997c) report the strongest

24   effects on peak flow were found with ultrafine particles. $PM_{MC\ 0.01-0.1}$: -1.21 (-2.13, -0.30);

25   $PM_{MC0.01-2.5}$: -1.01 (-1.92, -0.11); and PM_{10}, -1.30 (-2.36, -0.24).

26   Penttinen et al. (2001) using biweekly spirometry over 6 months on a group of 54 adult

27   asthmatics found that FVC, FEV_1, and spirometric PEFR were inversely, but mostly

28   nonsignificantly-associated with ultra fine particle concentrations. Compared to the effect

29   estimates for self-monitored PEFR, the effect estimates for spirometric PEFR tended to be larger.

30   The strongest associations were observed in the size range of 0.1 to 1 μm.

31

TABLE 8-23. SUMMARY OF ASTHMA PM$_{10}$ PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM$_{10}$
Asthma Studies					
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	1 day	1.39 (−0.57, 3.35)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	1 day	−4.70 (−7.65, -1.70)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	1 day	−0.65 (−3.97, 5.32)
Pekkanen et al. (1997)	Morning PEFR	14 (10, 23)	NO$_2$	0 day	−2.71 (−6.57, 1.15)
Peters et al. (1997a)	Morning PEFR	47 (29, 73)	SO$_2$, sulfate, H$^+$	1 day	−0.84 (−1.62, −0.06)
Peters et al. (1997c)	Morning PEFR	55 (?, 71)	SO$_2$, sulfate, H$^+$	1 day	−1.30 (−2.36, −0.24)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	2 day	0.34 (−1.78, 2.46)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	2 day	−4.90 (−8.40, -1.50)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	2 day	2.47 (−1.75, 6.75)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	0 day	−0.30 (−2.24, 1.64)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	0 day	−4.80 (−8.00, -1.70)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	0 day	−1.32 (−6.82, 4.17)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO$_2$	0 day	−0.35 (−4.31, 3.61)
Peters et al. (1996)	Evening PEFR	112	SO$_2$, sulfate, PSA	0 day	−1.03 (−1.98, −0.08)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO$_2$, sulfate, H$^+$	0 day	−0.92 (−1.96, 0.12)
Peters et al. (1997c)	Evening PEFR	55 (?, 71)	SO$_2$, sulfate, H$^+$	0 day	−0.37 (−1.82, 1.08)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO$_2$, SO$_2$	0 day	−1.10 (−5.20, 3.00)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO$_2$, SO$_2$	0 day	−1.66 (−8.26, 4.94)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	2 day	−2.32 (−5.36, 0.72)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	2 day	−3.65 (−7.20, 0.03)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	2 day	−0.04 (−4.29, 4.21)

TABLE 8-23 (cont'd). SUMMARY OF ASTHMA PM$_{10}$ PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM$_{10}$
Asthma Studies (cont'd)					
Segala et al. (1998)	Morning PEFR	34.2 (9, 95)	SO$_2$, NO$_2$	2 day	−0.62 (−1.52, 0.28)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO$_2$	2 day	0.14 (−6.97, 7.25)
Peters et al. (1997c)	Evening PEFR	55 (?, 71)	SO$_2$, sulfate, H$^+$	2 day	−2.31 (−4.53, −0.10)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO$_2$, SO$_2$	2 day	−1.13 (−4.75, 2.52)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO$_2$, SO$_2$	2 day	0.38 (−6.37, 7.13)
Peters et al. (1996)	Evening PEFR	112	SO$_2$, sulfate, PSA	5 day	−1.12 (−2.13, −0.10)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO$_2$, sulfate, H$^+$	1-5 day	−1.34 (−2.83, 0.15)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO$_2$, SO$_2$	1-4 day	−0.73 (−7.90, 6.44)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO$_2$, SO$_2$	1-4 day	−4.18 (−20.94, 12.58)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	1 day	−0.90 (−3.84, 2.04)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	2 day	−0.50 (−4.22, 3.22)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	1-7 day	−2.20 (−10.43, 6.03)
Vedal et al. (1998)	Ave. AM & PM	19.1 (1, 159)	None	1-4 day	−1.35 (−2.70, −.05)

TABLE 8-24. SUMMARY OF PM$_{2.5}$ PFT ASTHMA STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM$_{10}$
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	1 day	−3.65 (−8.25, 1.90)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	1 day	−0.71 (−1.30, 0.12)
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	2 day	−3.68 (−9.37, 2.00)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	1-5 day	−1.19 (−1.18, 0.57)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	0 day	−4.27 (−7.12, -0.85)
Peters et al. (1997c)	Evening PEFR	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	0 day	−0.75 (−1.66, 0.17)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	2 day	−2.55 (−7.84, 2.740
Peters et al. (1997c)	Evening PEFR	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	1-5 day	−1.79 (−2.64, -0.95)

1   In the Uniontown reanalysis, peak flow for $PM_{2.1}$ for a 14 $\mu g/m^3$ increment was -0.91 1/m

2    $(-1.14, -1.68)$ and $PM_{10-2.1}$ for 15 $\mu g/m^3$ $+1.04$ 1/m $(-1.32, +3.4)$; for State College $PM_{2.1}$ -0.56

3    $(-1.13, +0.01)$ and $PM_{10-2.1}$ -0.17 $(-2.07, +1.72)$. The Schwartz and Neas (2000) reanalyses

4   allows comparison of fine and coarse effects using two pollutant models for fraction of PM.

5   Coull et al. (2001) reanalyzed data from the Pope et al. (1991) study of PM effects on

6   pulmonary function of children in the Utah Valley, using additive mixed models which allow for

7   assessment of heterogeneity of response or the source of heterogeneity. These additive models

8   describe complex covariate effects on each child's peak expiratory flow while allowing for

9   unexplained population heterogeneity and serial correlation among repeated measurements. The

10   analyses indicates that there is heterogeneity in that population with regard to PM_{10} (i.e.,

11   specifically that there are three subjects in the Utah Valley study who exhibited a particularly

12   acute response to PM_{10}). However the limited demographic data available in the Utah Valley

13   Study does not explain the heterogeneity in PM sensitivity among the school children population.

14   The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10}

15   and $PM_{2.5}$. For PM_{10}, the available point estimates for morning PEF lagged one day showed

16   decreases, but the majority of the studies were not statistically significant, see Table 8-22 and as

17   shown in Figure 8-14 as an example of PEF outcomes. Lag 1 may be more relevant for morning

18   measurement of asthma outcome from the previous day. The figure presents studies which

19   provided such data. The results were consistent for both AM and PM peak flow analyses. The

20   effects using 2 to five-day lags averaged about the same as did the zero to one-day lags, but the

21   effects had wider confidence limits. Similar results were found for the $PM_{2.5}$ studies, although

22   there were fewer studies. Several studies included $PM_{2.5}$ and PM_{10} independently in their

23   analyses of peak flow. Of these, Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al.

24   (1997), and Romieu et al. (1996) all found similar results for $PM_{2.5}$ and PM_{10}. The study of

25   Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas

26   (2000) found larger effects for fine particle measures ($PM_{2.5}$, sulfate, etc.) than for the coarse

27   fraction. Naeher et al. (1999) found that H^+ was significantly related to a decrease in morning

28   PEF. Overall, then, PM_{10} and $PM_{2.5}$ both appear to affect lung function in asthmatics, but there is

29   only limited evidence for a stronger effect of fine versus coarse fraction particles. Also, of the

30   studies provided, few if any analyses were able to separate out the effects of PM_{10} and $PM_{2.5}$ from

31   other pollutants.
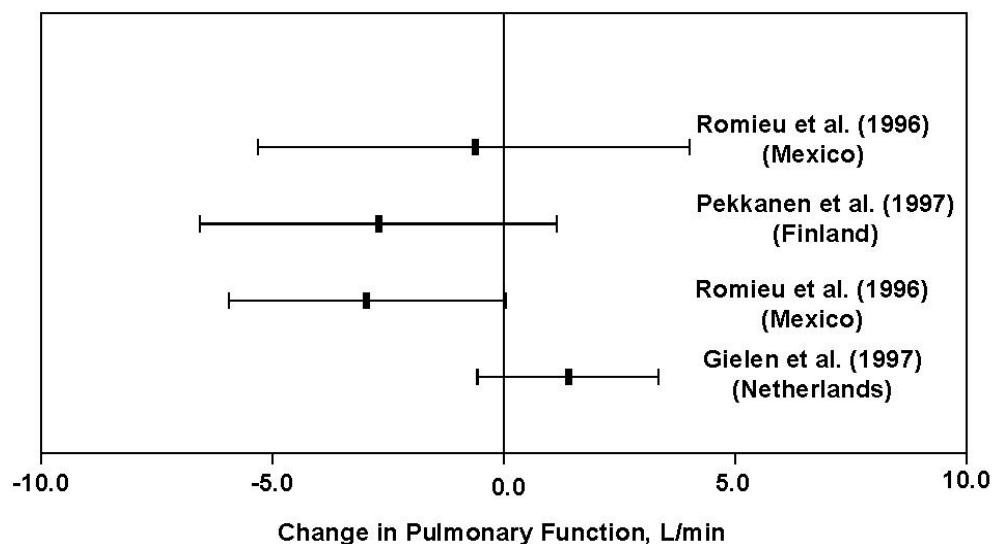
Figure 8-14. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 $\mu g/m^3$ PM_{10} on morning Peak flow lagged one-day.

1   The effects of PM on respiratory symptoms in asthmatics tended to be positive, although

2   they were much less consistent than the effects on lung function. Vedal et al. (1998) reported

3   that increases in PM_{10} were associated with increased reporting of cough, phlegm production, and

4   sore throat and that children with diagnosed asthma are more susceptible to the effects than are

5   other children. Similarly, in the Gielen et al. (1997) study of a panel of children, most of whom

6   had asthma, low levels of PM increased symptoms and medication use. Peters et al. (1997c)

7   study of asthmatics examined particle effects by size which indicated that fine particles were

8   associated with increases in cough, of which MC 0.01-2.5 was the best predictor.

9   Delfino et al. (1998) used an asthma symptom score to evaluate the effect of acute pollutant

10   exposures. PM_{10} 1- and 8-hr maximum had larger effects than the 24-hr mean. Subgroup

11   analyses showed effects of current day PM maximums were strongest in 10 more frequently

12   symptomatic children; the odds ratios for adverse symptoms from 90th percentile increases were

13   2.24 (1.46, 3.46), for 1-hr PM_{10}; 1.82 (1.18, 2.8), for 8-hr PM_{10}, and 1.50 (0.80-2.80) for 24-hr

14   PM_{10}. Analyses suggested that effects of O_3 and PM_{10} were largely independent.

15   Romieu et al. (1996) found children with mild asthma to be more strongly affected by high

16   ambient levels of PM observed in northern Mexico City than in a study (Romieu et al., 1997)

1   conducted in a nearby area with lower PM_{10} levels (mean $PM_{10} = 166.8$ $\mu g/m^3$ versus 54.2

2    $\mu g/m^3$). Yu et al. (2000) reported estimates of odd ratios for asthma symptoms and 10 $\mu g/m^3$

3   increments in PM_{10} and $PM_{1.0}$ values of 1.18 (1.05, 1.33) and 1.09 (1.01, 1.18), respectively.

4   Multipollutant models with CO and SO_2 yielded for PM_{10}, 1.06 (0.95, 1.19) for PM_{10}, and 1.11

5   (0.98, 1.26) for $PM_{1.0}$, thus showing a lower value for $PM_{1.0}$ and a lower value for PM_{10} with a

6   loss of significance. The correlation between CO and $PM_{1.0}$ and PM_{10} was 0.82 and 0.86. Ostro

7   et al. (2001) studied a panel of inner-city African American children using a GEE model with

8   several measures of PM, including PM_{10} (both 24-hour average and 1-hour max.) and $PM_{2.5}$,

9   demonstrating positive associations with daily probability of shortness of breath, wheeze, and

10   cough.

11   Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator

12   use, although these increases were generally not statistically significant for PM_{10} (see

13   Tables 8-25, 8-26, 8-27, and 8-28; and, for cough as an example, see Figure 8-15). For $PM_{2.5}$

14   results, see Table 8-29. Several studies included two indicators for PM; $PM_{10-2.5}$ or PM_{10} and

15   $PM_{2.5}$ in their analyses. The studies of Peters et al. (1997c) and Tiittanen et al. (1999) found

16   similar effects for the two PM measures, whereas the Romieu et al. (1996) study found slightly

17   larger effects for $PM_{2.5}$.

18

19   *8.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects*

20   Results of the PM_{10} peak flow analyses in non-asthmatic studies (see Appendix 8B, Table

21   8B-6) were inconsistent, with fewer studies reporting results in the same manner as for the

22   asthmatic studies (see Table 8-30). Many of the point estimates showed increases rather than

23   decreases. Similar results were found in the $PM_{2.5}$ studies (see Summary Table 8-31). The

24   effects on respiratory symptoms in non-asthmatics (see Appendix 8B, Table 8B-7) were similar

25   to those in asthmatics (see Table 8-32). Most studies showed that PM_{10} increases cough, phlegm,

26   difficulty breathing, and bronchodilator use, although these increases were generally not

27   statistically significant. For $PM_{2.5}$ see Tables 8-32 and for PM coarse studies see Table 8-33.

28   The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle effects

29   on healthy school children using two pollutant models of fine and coarse PM. CM was estimated

30   by subtracting $PM_{2.1}$ from PM_{10} data. They report for cough for reanalysis of the Harvard Six

31   City Diary Study in the two PM pollutant model $PM_{2.5}$ (increment 15 $\mu g/m^3$) OR = 1.07 (0.90,

TABLE 8-25. SUMMARY OF ASTHMA PM$_{10}$ COUGH STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 mg/m^3 PM$_{10}$
Asthma Studies					
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	0 day	1.40 (1.04, 1.88)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	0 day	2.19 (0.77, 6.20)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	0 day	0.93 (0.83, 1.04)
Peters et al. (1997c)	OR cough	55 (?, 71)	SO$_2$, sulfate, H$^+$	0 day	1.32 (1.16, 1.50)
Peters et al. (1997b)	OR cough	47 (29, 73)	SO$_2$, sulfate, H$^+$	0 day	1.01 (0.97, 1.07)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	0 day	1.05 (0.92, 1.18)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	0 day	1.27 (1.16, 1.42)
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	2 day	1.40 (1.13, 1.73)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	2 day	2.19 (0.47, 10.24)
Segala et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO$_2$, NO$_2$	2 day	(values not given because not significant)
Neukirch et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO$_2$, NO$_2$	3 day	(values not given because not significant)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	2 day	1.27 (1.07, 1.50)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	2 day	1.00 (0.92, 1.10)
Ostro et al. (2001)	OR cough	47 (11, 119) 24hr	Ozone, NO$_2$	3 day	1.32 (1.12, 1.55)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	1-7 day	0.94 (0.82, 1.08)
Peters et al. (1997c)	OR cough	55 (?, 71)	SO$_2$, sulfate, H$^+$	1-5 day	1.30 (1.09, 1.55)
Peters et al. (1997b)	OR cough	47 (29, 73)	SO$_2$, sulfate, H$^+$	1-5 day	1.10 (1.04, 1.17)
Ostro et al. (2001)	OR cough	102 (47, 360) 1 hr max	ozone, NO$_2$	3 day	1.05 (1.02, 1.18)

TABLE 8-26. SUMMARY OF ASTHMA PM$_{10}$ PHLEGM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-Pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m^3 PM$_{10}$
Vedal et al. (1998)	OR Phlegm	19.1 (1, 159)	None	0 day	1.28 (0.86, 1.89)
Peters et al. (1997b)	OR Phlegm	47 (29, 73)	SO$_2$, sulfate, H$^+$	0 day	1.13 (1.04, 1.23)
Romieu et al. (1997)	OR Phlegm	(12, 126)	Ozone	0 day	1.05 (0.83, 1.36)
Romieu et al. (1996)	OR Phlegm	166.8 (29, 363)	Ozone	0 day	1.21 (1.00, 1.48)
Vedal et al. (1998)	OR Phlegm	19.1 (1, 159)	None	2 day	1.40 (1.03, 1.90)
Romieu et al. (1997)	OR Phlegm	(12, 126)	Ozone	2 day	1.00 (0.86, 1.16)
Romieu et al. (1996)	OR Phlegm	166.8 (29, 363)	Ozone	2 day	1.16 (0.91, 1.49)
Peters et al. (1997b)	OR Phlegm	47 (29, 73)	SO$_2$, sulfate, H$^+$	1-5 day	1.17 (1.09, 1.27)

TABLE 8-27. SUMMARY OF ASTHMA PM10 LOWER RESPIRATORY ILLNESS (LRI) STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range)	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m^3 PM$_{10}$
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	0 day	1.10 (0.82, 1.48)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	0 day	1.26 (0.94, 1.68)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	0 day	1.00 (0.95, 1.05)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	0 day	1.21 (1.10, 1.42)
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	2 day	1.16 (1.00, 1.34)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	2 day	1.05 (0.74, 1.48)
Segala et al. (1998)	LRI	34.2 (9, 95)	SO$_2$, NO$_2$	2 day	1.66 (0.84, 3.30)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	2 day	1.00 (0.93, 1.08)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	2 day	1.10 (0.98, 1.24)
Delfino et al. (1998)	LRI	24 h 26 (6, 51) 8-h 43 (23-73) 1-h 57 (30-108)	Ozone Ozone Ozone	0 day 0 day 0 day	1.47 (0.90 - 2.39) 2.17 (1.33 - 3.58) 1.78 (1.25 - 2.53)

TABLE 8-28. SUMMARY OF ASTHMA PM$_{10}$ BRONCHODILATOR USE STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m^3 PM$_{10}$
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	0 day	0.94 (0.59, 1.50)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	0 day	1.03 (0.93, 1.15)
Peters et al. (1997b)	OR bronchodilator use	47 (29, 73)	SO$_2$, sulfate, H$^+$	0 day	1.06 (0.88, 1.27)
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	2 day	2.90 (1.81, 4.66)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO$_2$, SO$_2$	1-7 day	1.12 (1.00, 1.25)
Peters et al. (1997b)	OR bronchodilator use	47 (29, 73)	SO$_2$, sulfate, H$^+$	1-5 day	1.23 (0.96, 1.58)
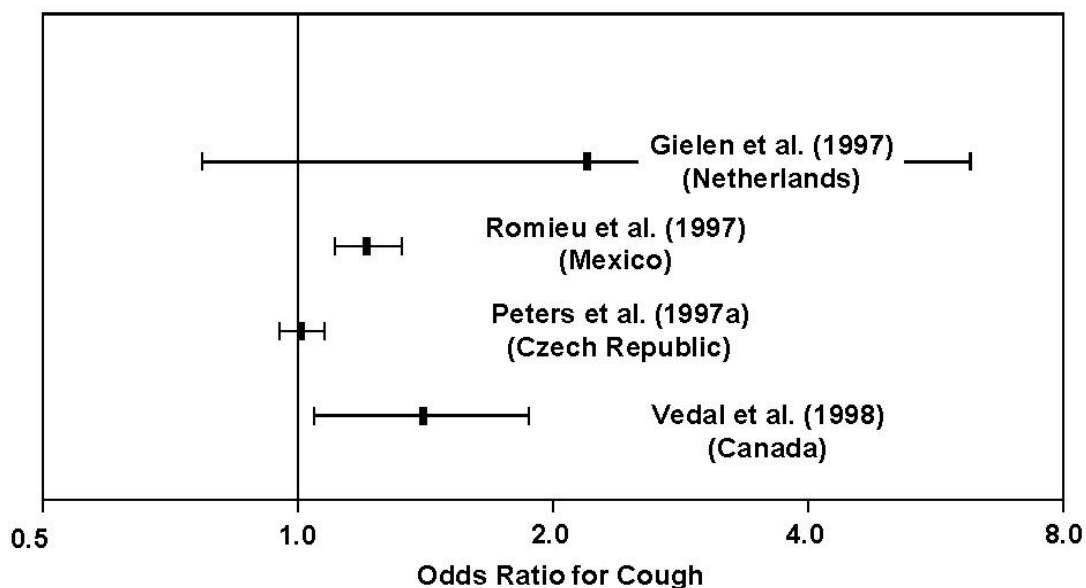
Figure 8-15. Odds ratios with 95% confidence interval for cough per 50-μg/m^3 increase in PM$_{10}$ for selected asthmatic children studies at lag 0.

1.26) and PM$_{10-2.5}$ (increment 8 μg/m^3) OR 1.18 (1.04, 1.34) in contrast to lower respiratory

symptom results of PM$_{2.5}$ OR 1.29 (1.06, 1.57) and PM$_{10-2.5}$ 1.05 (0.9, 1.23).

Jalaludin et al. (2000) analyses using a multipollutant model evaluated O$_3$, PM$_{10}$, and NO$_2$.

They found in metropolitan Sydney that ambient ozone and PM$_{10}$ concentrations are poorly

correlated (0.13). For PEFR PM$_{10}$ only was 0.0045 (0.0125) p-0.72, and with O$_3$, 0.0051

(0.0124), p-0.68. Ozone was also unchanged in the one- and two-pollutant models. Gold et al.

(1999) attempted to study the interaction of PM$_{2.5}$ and ozone on PEF. The authors found

independent effects of the two pollutants, but found that the joint effect was slightly less than the

sum of the independent effects.

Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999),

used PM$_{10-2.5}$ as a coarse fraction particulate measure. Schwartz and Neas (2000) found that PM$_{10}$

was significantly related to cough. Tiittanen found that one day lag of PM$_{10-2.5}$ was related to

morning PEF, but there was no effect on evening PEF. Neas et al. found no effects of PM$_{10-2.5}$ on

PEF.

TABLE 8-29. SUMMARY OF ASTHMA PM$_{2.5}$ RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu g/m^3$ PM$_{2.5}$
Peters et al. (1997b)	OR cough	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	0 day	1.22 (1.08, 1.38)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	0 day	1.27 (1.08, 1.42)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO$_2$, SO$_2$, CO, ozone	0 day	1.04 (0.86, 1.20)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	2 day	1.16 (0.98, 1.33)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO$_2$, SO$_2$, CO, ozone	2 day	1.24 (1.02, 1.51)
Ostro et al. (2001)	OR cough	40.8 (4, 208)	Ozone, NO$_2$	3 day	1.02 (0.98, 1.06)
Peters et al. (1997b)	OR cough	50.8 (9, 347)	SO$_2$, sulfate, H$^+$	1-5 day	1.02 (0.90, 1.17)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	0 day	1.21 (0.98, 1.48)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	2 day	1.16 (0.99, 1.39)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	0 day	1.21 (1.05, 1.42)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	2 day	1.16 (1.05, 1.42)

1 **8.3.3.2   Long-Term Particulate Matter Exposure Effects on Lung Function and**
2 **Respiratory Symptoms**

3 *8.3.3.2.1 Summary of the 1996 Particulate Matter Air Quality Criteria Document Key*
4 *Findings*

5   In the 1996 PM AQCD, the available long-term PM exposure-respiratory disease studies

6 were limited in terms of conclusions that could be drawn. At that time, three studies based on a

7 similar type of respiratory symptom questionnaire administered at three different times as part of

8 the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory

9 disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory

10 disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly

11 positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using

TABLE 8-30. SUMMARY OF NON-ASTHMA PM$_{10}$ PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM$_{10}$
Gold et al. (1999)	Morning PEFR	51 (23, 878)	Ozone	1 day	−0.20 (−0.47, 0.07)
Tittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	0 day	1.21 (−0.43, 2.85)
Neas et al. (1999)	Morning PEFR	32	Ozone	1-5 day	2.64 (−6.56, 11.83)
Tittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	1-4 day	−1.26 (−5.86, 3.33)
Boezen et al. (1999)	OR >10% AM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	1 day	1.04 (0.95, 1.13)
Boezen et al. (1999)	OR >10% AM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	2 day	1.02 (0.93, 1.11)
Boezen et al. (1999)	OR >10% AM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	1-5 day	1.05 (0.91, 1.21)
Neas et al. (1999)	Morning PEFR	32	Ozone	0 day	−8.16 (−14.81, −1.55)
Harré et al. (1997)	% change in morning PEFR	(not given)	NO$_2$, SO$_2$, CO	1 day	0.07 (−0.50, 0.63)
Neas et al. (1999)	Evening PEFR	32	Ozone	0 day	−1.44 (−7.33, 4.44)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	0 day	0.72 (−0.63, 1.26)
Tittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	0 day	2.33 (−2.62, 7.28)
Gold et al. (1999)	Evening PEFR	51 (23, 878)	Ozone	0 day	−0.14 (−0.45, 0.17)
Neas et al. (1999)	Evening PEFR	32	Ozone	1-5 day	1.47 (−7.31, 10.22)
Boezen et al. (1999)	OR >10% PM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	0 day	1.17 (1.08, 1.28)
Boezen et al. (1999)	OR >10% PM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	2 day	1.08 (0.99, 1.17)
Boezen et al. (1999)	OR >10% PM PEFR Decr.	42 (5, 146)	NO$_2$, SO$_2$	1-5 day	1.16 (1.02, 1.33)
Van der Zee et al. (1999)	OR >10% PM PEFR Decr.	34 (?, 106)	NO$_2$, SO$_2$, sulfate	0 day	1.44 (1.02, 2.03)
Van der Zee et al. (1999)	OR >10% PM PEFR Decr.	34 (?, 106)	NO$_2$, SO$_2$, sulfate	2 day	1.14 (0.83, 1.58)
Van der Zee et al. (1999)	OR >10% PM PEFR Decr.	34 (?, 106)	NO$_2$, SO$_2$, sulfate	1-5 day	1.16 (0.64, 2.10)
Harré et al. (1997)	% change in evening PEFR	(not given)	NO$_2$, SO$_2$, CO	1 day	−0.22 (−0.57, 0.16)

TABLE 8-31. SUMMARY OF NON-ASTHMA PM$_{10}$ RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 mg/m^3 PM$_{10}$
Schwartz & Neas (2000)	OR cough–no other symptoms	(not given)	Sulfate fraction	0 day	1.20 (1.07, 1.35)
Boezen et al. (1998)	OR cough	42 (5, 146)	NO$_2$, SO$_2$	0 day	1.06 (0.93, 1.21)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO$_2$, SO$_2$, sulfate	0 day	1.04 (0.95, 1.14)
Tittanen et al. (1999)	OR cough	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	0 day	1.00 (0.87, 1.16)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO$_2$, SO$_2$, sulfate	2 day	0.94 (0.89, 1.06)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO$_2$, SO$_2$, sulfate	1-5 day	0.95 (0.80, 1.13)
Tittanen et al. (1999)	OR cough	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	1-4 day	1.58 (0.87, 2.83)
Boezen et al. (1998)	OR Phlegm	42 (5, 146)	NO$_2$, SO$_2$	0 day	1.11 (0.91, 1.36)
Tittanen et al. (1999)	OR Phlegm	28 (5, 122)	NO$_2$, SO$_2$, CO, ozone	2 day	Positive but not significant
Schwartz & Neas (2000)	LRI	(not given)	Sulfate fraction	0 day	
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO$_2$, SO$_2$, sulfate	0 day	0.98 (0.89, 1.08)
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO$_2$, SO$_2$, sulfate	2 day	1.01 (0.93, 1.10)

**TABLE 8-32. SUMMARY OF NON-ASTHMA PM$_{2.5}$ RESPIRATORY OUTCOME STUDIES**

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 μg/m^3 PM$_{2.5}$
Gold et al. (1999)	Morning PEFR	30.3 (9, 69)	Ozone	1 day	−0.22 (−0.46, 0.01)
Tittanen et al. (1999)	Morning PEFR		NO$_2$, SO$_2$, CO, ozone	0 day	1.11 (−0.64, 2.86)
Tittanen et al. (1999)	Morning PEFR		NO$_2$, SO$_2$, CO, ozone	1-4 day	−1.93 (−7.00, 3.15)
Neas et al. (1999)	Morning PEFR	24.5 (?, 88)	Ozone	1-5 day	2.64 (−6.56, 11.83)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tittanen et al. (1999)	Evening PEFR		NO$_2$, SO$_2$, CO, ozone	0 day	0.70 (−0.81, 2.20)
Tittanen et al. (1999)	Evening PEFR		NO$_2$, SO$_2$, CO, ozone	0 day	1.52 (−3.91, 6.94)
Gold et al. (1999)	Evening PEFR	30.3 (9, 69)	Ozone	0 day	−0.10 (−0.43, 0.22)
Neas et al. (1999)	Evening PEFR	24.5 (?, 88)	Ozone	1-5 day	1.47 (−7.31, 10.22)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO$_2$, SO$_2$, CO, ozone	0 day	1.04 (0.86, 1.20)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO$_2$, SO$_2$, CO, ozone	2 day	1.24 (1.02, 1.51)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.61 (1.19, 2.14)

TABLE 8-33. SUMMARY OF NON-ASTHMA COARSE FRACTION STUDIES OF RESPIRATORY ENDPOINTS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu g/m^3$ $PM_{10-2.5}$
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1 day	−1.26 (−2.71, 0.18)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1 day	−4.31 (−11.43, 2.75)
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.51 (−0.77, 2.16)
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	−0.57 (−1.96, 0.81)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1-5 day	−6.37 (−21.19, 8.44)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.66 (−0.33, 1.81)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1 day	1.88 (−4.75, 8.44)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.03 (−1.41, 1.47)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	2.37 (−1.69, 4.96)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1-5 day	5.94 (−7.00, 18.94)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.99 (0.87, 1.12)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	1.23 (1.06, 1.42)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	1.31 (0.81, 2.11)
Schwartz & Neas (2000)	OR cough without other symptoms	(not given)	Sulfate fraction	0 day	1.77 (1.24, 2.55)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.51 (0.94, 4.87)

1   a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include

2   24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio

3   = 1.66) in the community with the highest particle strong acidity when compared with the least

4   polluted community. Fine particulate sulfate was also associated with higher reporting of

5   bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

6   Interpretation of such studies requires caution in light of the usual difficulties ascribed to

7   cross-sectional studies. That is, evaluation of PM effects is based on variations in exposure

8   determined by a different number of locations. In the first two studies, there were six locations

9   and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient,

10   but it was impossible to separate out effects of PM and any other factors or pollutants having the

11   same gradient.

12   Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas

13   et al. (1994) had good monitoring data and well-conducted standardized pulmonary function

14   testing over many years, but showed no effect for children from airborne particle pollution

15   indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study of U.S. and

16   Canadian children found significant associations between FEV_1 and FVC and acidic particles

17   (H^+). Overall, the available studies provided only limited evidence suggestive of pulmonary lung

18   function decrements being associated with chronic exposure to PM indexed by various measures

19   (TSP, PM_{10}, sulfates, etc.). However, it was noted that cross-sectional studies require very large

20   sample sizes to detect differences because they cannot eliminate person to person variation,

21   which is much larger than the within person variation.

22

23   *8.3.3.2.2 New Studies of Long-Term Particulate Matter Exposure Respiratory Effects*

24   Several studies have been published since 1996 which evaluate effects of long-term PM

25   exposure on lung function and respiratory illness, as summarized in Appendix 8B, Table 8B-8.

26   The new studies examining PM_{10} and $PM_{2.5}$ in the United States include McConnell et al. (1999),

27   Abbey et al. (1998), Berglund et al. (1999), Peters et al. (1999a,b), Gauderman et al. (2000), and

28   Avol et al. (2001), which all examined effects in California cohorts but produced inconsistent

29   results. McConnell et al. (1999) noted that as PM_{10} increased across communities, an increase in

30   bronchitis risk per interquartile range also occurred, results consistent with those reported by

31   Dockery et al. (1996), although the high correlation of PM_{10}, acid, and NO_2 precludes clear

1   attribution of the McConnell et al. bronchitis effects specifically to PM alone. Avol et al. (2001)

2   reported that, for 110 children that moved to other locations as a group, subjects who moved to

3   areas of lower PM_{10} showed increased growth in lung function and subjects who moved to

4   communities with higher PM_{10} showed slowed lung function growth.

5   For non-U.S. studies, particularly interesting results were obtained by Leonardi et al. (2000)

6   as part of the Central European Air Quality and Respiratory Health (CESAR) study. Blood and

7   serum samples were collected from school children aged 9-11 yrs. in each of 17 communities in

8   Central Europe (N = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations

9   increased across the cities. Regression slopes, adjusted for confounder effects, were largest and

10   statistically significant for $PM_{2.5}$, but small and non-significant for $PM_{10-2.5}$. A similar positive

11   relationship was found between IgG concentration in serum and $PM_{2.5}$ gradient, but not for PM_{10}

12   or $PM_{10-2.5}$. These results tend to suggest a PM effect on immune function more strongly due to

13   ambient fine particle than coarse particle exposure.

14   Other non-U.S. studies examined PM measures such as TSP and BS in European countries.

15   In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted twice

16   (with the same 971 children included in both surveys). TSP levels decreased between surveys as

17   did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer et al. (1999)

18   reported a study in six East and West Germany communities, which found yearly decreasing TSP

19   levels to be related to ever-diagnosed bronchitis from 1991-1995. Lastly, Jedrychowski et al.

20   (1999) reported an association between both BS and SO_2 levels in various areas of Krakow,

21   Poland, and slowed lung function growth (FVC and FEV_1).

22

23   *8.3.3.2.3 Summary of Long-Term Particulate Matter Exposure Respiratory Effects*

24   The methodology used in the long-term studies varies much more than the methodology in

25   the short-term studies. Some studies reported highly significant results (related to PM) while

26   others reported no significant results. The cross-sectional studies are often confounded, in part,

27   by unexplained differences between geographic regions. The studies that looked for a time trend

28   are also confounded by other conditions that were changing over time. Probably the most

29   credible cross-sectional study remains that described by Dockery et al. (1996) and Raizenne et al.

30   (1996). This study, reported in the previous 1996 PM AQCD, found differences in peak flow

31   and bronchitis rates associated with fine particle strong acidity.

1   Newly available studies since the 1996 PM AQCD, overall, provide evidence consistent

2   with the findings from the above 24-City Study. Most notably, several U.S. and European

3   studies report associations between PM measures and bronchitis rates and/or lung function

4   decrements or slowed lung function growth. One also provided evidence of PM effects on

5   immune function in school children, with stronger associations for fine particle indicators than

6   for ambient coarse particles.

7

8

8.4 DISCUSSION OF EPIDEMIOLOGIC STUDIES ON HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER

8.4.1 Introduction

12   Numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient

13   PM as a likely contributor to mortality and morbidity effects associated with ambient air

14   pollution exposures in epidemiology studies. Since preparation of the last previous PM AQCD

15   in 1996, the epidemiologic evidence concerning ambient PM-related health effects has expanded

16   greatly. Past regulatory decisions have played an important role in the selection of PM indices

17   and in the evolution of the PM epidemiologic literature base. The adoption of PM_{10} standards in

18   1987, and of $PM_{2.5}$ standards in 1997, have generated ambient air concentration databases that

19   made it possible for research to address and resolve many of previously unresolved linkages

20   between airborne PM and human health; and the newly authorized network of speciation

21   samplers holds promise for further advances in the near future on the identification of the more

22   influential components of the ambient air pollution mixture. The most important types of

23   additions to the database beyond that assessed in the 1996 PM AQCD, as evaluated above in this

24   chapter, are:

25

26   (1) New multi-city studies on a variety of endpoints which provide more precise estimates of the

27   average PM effect sizes than most smaller-scale individual city studies, but also showing much

28   greater heterogeneity among studies than previously observed;

29

1   (2) More studies of various health endpoints using ambient PM_{10} and/or closely related mass

2   concentration indices (e.g., PM_{13} and PM_7), which substantially lessen the need to rely on

3   non-gravimetric indices (e.g., BS or COH);

4

5   (3) New studies evaluating relationships of a variety of endpoints to the ambient PM coarse

6   fraction ($PM_{10-2.5}$), the ambient fine-particle fraction ($PM_{2.5}$), and even ambient ultrafine particles

7   measures ($PM_{0.1}$ and smaller) using direct mass measurements and/or estimated from site-specific

8   calibrations;

9

10   (4) A few new studies in which the relationship of some health endpoints to ambient particle

11   number concentrations were evaluated;

12

13   (5) Many new studies which evaluated the sensitivity of estimated PM effects to the inclusion of

14   gaseous co-pollutants in the model;

15

16   (6) Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures

17   including PM components, based on empirical combinations (e.g., factor analysis) or source

18   profiles;

19

20   (7) Numerous new studies of cardiovascular endpoints, with particular emphasis on assessment

21   of cardiovascular risk factors as well as symptoms;

22

23   (8) Additional new studies on asthma and other respiratory conditions potentially exacerbated by

24   PM exposure;

25

26   (9) New analyses of lung cancer associations with long-term exposures to ambient PM.

27

28   (10) New studies of infants and children as a potentially susceptible population.

29

30   As discussed in Sections 8.2 and 8.3, numerous new PM epidemiology studies, both of

31   short-term and long-term PM exposure, show statistically significant excess risk for various

1   mortality and/or morbidity endpoints in many U.S. cities and elsewhere to be associated with

2   ambient PM indexed by a variety of ambient community monitoring methods.

3   Still, several methodological issues discussed in the 1996 PM AQCD continue to be

4   important in assessing and interpreting the overall PM epidemiology database and its

5   implications for estimating risks associated with exposure to ambient PM concentrations in the

6   United States. The fundamental issue essentially subsuming all of the other modeling issues is

7   the selection of an appropriate statistical model. These critical methodological issues are:

8   (1) potential confounding of PM effects by co-pollutants (especially major gaseous pollutants

9   such as O_3, CO, NO_2, SO_2); (2) the attribution of PM effects to specific PM components (e.g.,

10   PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafines, sulfates, metals, etc.) or source-oriented indicators (motor

11   vehicle emissions, vegetative burning, etc.); (3) the temporal relationship between exposure and

12   effect (lags, mortality displacement, etc.); (4) the general shape of exposure-response

13   relationship(s) between PM and/or other pollutants and observed health effects (e.g., potential

14   indications of thresholds for PM effects); and (5) the consequences of measurement error.

15   Assessing the above issue(s) in relation to the PM epidemiology data base remains quite a

16   challenge. The basic issue is that there are an extremely large number of possible models, any of

17   which may turn out to give the best statistical "fit" of a given set of data, and only some of which

18   can be dismissed *a priori* as biologically or physically illogical or impossible, except that

19   putative cause clearly cannot follow effect in time. Most of the models for daily time series

20   studies are fitted by adjusting for changes over long time intervals and across season, by day of

21   week, weather, and climate. Many of the temporal and weather variable models have been fitted

22   to data using semi-parametric methods such as spline functions or local regression smoothers

23   (loess). The goodness of fit of these base models has been evaluated by criteria suitable for

24   generalized linear models with Poisson or hyper-Poisson responses (number of events) with a log

25   link function, particularly the Akaike Information Criterion (AIC) and the more conservative

26   Bayes or Schwarz information criterion (BIC), which adjust for the number of parameters

27   estimated from the data. The Poisson over-dispersion index and the auto-correlation of residuals

28   are also often used. It is often assumed, but rarely proven, that the best-fitting models with PM

29   would be models with the largest and most significant PM indices. Also, if high correlations

30   between PM and one or more gaseous pollutants emitted from a common source (e.g., motor

31   vehicles) exist in a given area, then disentangling their relative individual partial contributions to

1   observed health effects associations becomes very difficult. However, there have been very few

2   attempts at broad, systematic investigations of the model selection issue and little reporting of

3   goodness-of-fit criteria among competing models that provide a better basis by which to better

4   assess or compare models.

5   One systemic analysis of model choice was carried out by Clyde et al. (2000), using

6   Bayesian Model Averaging for the same Birmingham, AL, data as analyzed by Smith et al.

7   (2000). Several different calibrated information criterion priors were tried in which models with

8   large numbers of parameters are penalized to various degrees. After taking out a baseline trend

9   (estimated using a GLM estimate with a 30-knot thin-plate smoothing spline), 7,860 models were

10   selected for use in model averaging. These included lags 0-3 of a daily monitor PM_{10}, an

11   area-wide average PM_{10} value with the same lags, temperature (daily extremes and average)

12   lagged 0-2 days, humidity (dewpoint, relative humidity min and max, average specific humidity)

13   lagged 0-2, and atmospheric pressure, lagged 0-2. The model choice is sensitive to the

14   specification of calibrated information criterion priors, in particular disagreeing as to whether

15   different PM_{10} variables should be included or not. For example, one or another PM_{10} variable is

16   included in all the top 25 Akaike Information Criterion (AIC) models, but only in about 1/3 of

17   the top Bayes Information Criterion (BIC) models. Both approaches give a relative risk estimate

18   of about 1.05 (to be compared to the Schwartz value of 1.11 for a 100 unit increase), with

19   credibility intervals of (0.94, 1.17) for the AIC prior and (0.99, 1.11) for the BIC prior.

20   A validation study in which randomly selected data were predicted using the different priors

21   favored Bayesian model averaging with BIC prior over model selection (picking the best model)

22   with BIC or any approach with AIC. This method could be useful in assessing multi-pollutant

23   models.

24   The possibility that an observed effect is "real" (i.e., likely to be found in an independent

25   replication of the study) or merely a statistical artifact is usually characterized by its confidence

26   interval or by its estimated significance level. In most of this document, confidence intervals, or

27   credible intervals for Bayesian analyses, are reported in order to emphasize that the effect size is

28   not known with certainty, but some values are more nearly consistent with the data than effect

29   size values outside the interval. P-values or t-values are implicitly associated with a null

30   hypothesis of no effect. A nominal significance level of 5% (i.e., a 95% confidence interval) is

31   usually used as a guide for the reader, but P-values should not be used as a rigid decision-making

1   tool. If the observed confidence intervals were arrived at by a number of prior model

2   specification searches, eliminating some worse fitting models, the true interval may well be

3   wider.

4   Given the now extremely large number of published epidemiologic studies of ambient PM

5   associations with health effects in human populations and the considerably wide diversity in

6   applications of even similar statistical approaches (e.g., "time-series analyses" for short-term PM

7   exposure effects), it is neither feasible nor useful here to try to evaluate the methodological

8   soundness of every individual study. Rather, two feasible approaches are likely to yield useful

9   evaluative information: (1) an overall characterization of evident general commonalities (and/or

10   notable marked differences) among findings from across the body of studies dealing with

11   particular PM exposure indices and types of health outcomes; and (2) more thorough, critical

12   assessment of key newly published multi-city analyses of PM effects, given that greater scientific

13   weight is likely ascribable to their results than those of smaller sized studies (often of individual

14   cities) yielding presumably less precise effects estimates. However, while pooling estimates

15   across cities may give more precise estimates of mean effect size, the uncertainty in the estimated

16   mean effect may also be inflated by differences in effect size among cities.

17   In the sections that follow, each of the five issues listed above (e.g., potential confounding

18   of PM effects by co-pollutants and so on) are critically discussed. In addition, given that the

19   newer multi-city study results, e.g, the NMMAPS analysis of the 90 largest U.S. cities (Samet

20   et al., 2000a,b) show evidence of more geographical heterogeneity in the estimated PM risks

21   across cities and regions than had been seen in the studies assessed in the 1996 PM AQCD, the

22   issue of geographical heterogeneity in PM effects estimates also warrants further evaluation here

23   (as is done in Section 8.4.9).

24

25   **8.4.2 Assessment of Confounding by Co-Pollutants**

26   **8.4.2.1 Introduction**

27   Airborne particles are found among a complex mixture of atmospheric pollutants, some of

28   which are well measured (such as gaseous criteria co-pollutants O_3, CO, NO_2, SO_2) and others

29   which are not routinely measured. The basic question here is one of determining the extent to

30   which observed health effects can be attributed to airborne particles acting alone or in

31   combination with other air pollutants. Many of the pollutants are closely correlated due to

1   emissions by common sources and dispersion by common meteorological factors (so that it may

2   be difficult to disentangle their effects (as noted in Section 8.1.1), because some are in the

3   pathway of formation of other pollutants, e.g.: $NO \rightarrow NO_2 \rightarrow NO_3^{-1} \rightarrow$ Particle Mass.

4   It is widely accepted that some PM metrics are associated with health effects, and that PM

5   has effects independent of the gaseous co-pollutants. The extent to which ambient gaseous

6   co-pollutants may have health effects independent of PM is less certain, but this is important in

7   considering the extent to which health effects attributed to PM may actually be due in part to

8   co-pollutants or to some other environmental factors, and conversely. EPA produces Air Quality

9   Criteria Documents for four gaseous pollutants: CO, NO_2, SO_2, and O_3. The possible health

10   effects of the gaseous pollutants exerted independently from PM, and in some cases jointly with

11   PM, are discussed in those documents. They are also considered to some extent in this section

12   and elsewhere in this document because they affect quantitative assessments of the effects of

13   various PM metrics when these other pollutants are also present in the atmosphere. The gaseous

14   pollutants may also be of interest as PM effect modifiers, or through interactions with PM.

15   Co-pollutant models have received a great deal of attention in the last few years because

16   there now exist improved statistical methods for estimating PM effects by analyses of daily time

17   series of mortality (Schwartz and Marcus, 1990; Schwartz, 1991) or hospital admissions

18   (Schwartz, 1994) and/or in prospective cohort studies (Dockery et al., 1993). For example, in the

19   most recent AQCD for NO_2 (U.S. EPA, 1993), there are only three epidemiology studies on

20   mortality, a daily time series study (Lebowitz, 1971) and two ecological analyses (Hickey et al.,

21   1970; Mendelsohn and Orcutt, 1979). The results of these earlier studies are described by U.S.

22   EPA (1993) as non-significant or inconclusive. By comparison, many of the studies using the

23   new methods have found significant positive relationships between mortality and one or more of

24   the four gaseous criteria pollutants in daily time series studies, and between SO_2 and mortality in

25   the reanalyses of two large prospective cohort studies (Krewski et al., 2000). In the daily time

26   series studies, the estimated PM effect is relatively stable when the co-pollutant is included in the

27   model in some cities, whereas the estimated PM effect in other cities changes substantially when

28   certain co-pollutants are included. In the Krewski et al. (2000) analyses, the estimated effect of

29   $SO_4^=$ is greatly decreased when SO_2 is also included as a predictor in a proportional hazards

30   model. How should these findings be interpreted?

1   A number of the analyses presented below also discuss models in which multiple particle

2   metrics are present, either with or without the gaseous criteria pollutants. These mixtures are

3   encountered in urban air. Included among the studies evaluating both fine and coarse particles

4   simultaneously are: Burnett et al. (2000), Chock et al. (2000), Clyde et al. (2000), Fairley et al.

5   (1999), Lippmann et al. (2000), Mar et al.(2000); Cifuentes et al. (2001), and Castillejos et al.

6   (2000).

7   Gaseous co-pollutant levels may be correlated with total PM mass, but may be even more

8   strongly correlated with specific PM constituents due to their emission from a common source

9   (e.g., CO and NO_2 from motor vehicle exhaust). The levels of a specific gaseous co-pollutant

10   may serve as an indicator of the day-to-day variation in the contribution of a distinct emission

11   source and to the varying composition of airborne PM. In a model with total PM mass, a gaseous

12   co-pollutant may serve as a surrogate for the source-apportioned contribution to ambient air PM.

13   It would be interesting to evaluate models with both source-relevant particle components (e.g.,

14   attributable to motor vehicles, coal combustion, oil combustion) and gaseous pollutants. The

15   closest approach is Model II in Burnett et al. (2000).

16   Carbon monoxide and NO_2 may be acting as indicators of distinct emission sources

17   (primarily motor vehicles) and as indicators of PM from these sources (primary particles and

18   secondary nitrate particles). However, there are other sources of NO_2, such as emissions from

19   coal- or oil-burning electric power plants.

20   The role of gaseous pollutants as surrogates for source-apportioned PM may be distinct

21   from confounding. The true health effect may be independently associated with a particular

22   ambient PM constituent that may be more or less toxic than the particle mix as a whole. Thus,

23   a gaseous co-pollutant may give rise to the appearance of confounding in a regression model.

24   By serving as an indicator of the more toxic particles, the gaseous co-pollutant could greatly

25   diminish the coefficient for total particle mass. In such a model, the coefficient for total particle

26   mass would most properly be interpreted an indicator of the other, less-toxic particles. The

27   conceptual issues in evaluating potential confounding are at least as complex as the technical

28   aspects discussed below. We restrict our discussion to daily time series studies.

29

30

31

1 The conceptual problems in answering the question about confounding are:

2

3 (a) Biological plausibility: Can some of the gaseous criteria pollutants cause increases in

4 mortality or hospital admissions rates in the (presumably most susceptible) sub-populations at

5 current levels of exposure to ambient concentrations? If so, are these increases in mortality or

6 hospital admissions likely to be associated with cardiovascular or respiratory causes?

7

8 (b) Exposure plausibility: Do some members of the population have personal exposure to both

9 the particle metrics of ambient origin and the gaseous pollutants of ambient origin? Also, do

10 susceptible subpopulations have greater or smaller personal exposure to ambient particles or

11 gases than the population as a whole?

12

13   The technical problems in answering these question(s) are:

14

15 (c) Is the model mis-specified (omission of predictive regressors, inclusion of correlated but non-

16 predictive regressors, non-linearity, lags, measurement error from use of proxy variables)?

17

18 (d) Is there a bias in effect size estimates as a result of model mis-specification?

19

20 (e) Are the estimates of effect size standard errors sensitive to model mis-specification?

21

22 (f) Do some of the mis-specification errors compound each other, e.g., non-linearity combined

23 with measurement error?

24

25 (g) Are effect size estimates and their standard errors really significantly different among

26 models?

27

28

29

1 **8.4.2.2 Issues**

2 *8.4.2.2.1 Conceptual Issues in Assessing Confounding*

3   These concerns overlap two of Hill's (1965) suggested criteria for causal inference.

4   (a) <u>Biological plausibility</u>: It is generally accepted that O_3, NO_2, and SO_2 are associated

5 with diminished pulmonary function and increased respiratory symptoms as well as more serious

6 consequences, and CO exposure has been associated with cardiovascular effects. While one may

7 question whether adverse health effects occur in most healthy people at current exposure to

8 ambient concentrations, there may be a susceptible sub-population for whom ambient gaseous

9 pollutants cause health effects. One should remember that less than 20 years ago, current levels

10 of exposure to ambient concentrations of PM were thought to be safe. It would be premature to

11 conclude that the gaseous co-pollutants at current ambient levels are not associated with

12 respiratory and cardiovascular health effects in susceptible subpopulations.

13   Ambient gaseous co-pollutants can be potential confounders of ambient PM if: (a) both the

14 gas and PM are able to cause the same health effects; (b) if personal exposure is correlated with

15 ambient concentrations for both particles and gases respectively; (c) if the personal exposure to

16 gases and to particles are correlated, and; (d) if the ambient concentrations of particles and gases

17 are correlated. If any of these conditions fail, then we may have any of the conditions called

18 "under-fitting", "over-fitting", or "mis-fitting" described in Section 8.4.2.2.2.

19   (b) <u>Exposure plausibility</u>: While most Americans spend most of their time in indoor

20 microenvironments, there is still sufficient personal exposure to O_3 to cause frank respiratory

21 symptoms among sensitive children or adults exercising outdoors when ambient O_3

22 concentrations are high (hence the declaration of "ozone alert" days). It is also likely that some

23 fraction of ambient CO also contributes to indoor air pollution and total personal CO exposure.

24 Nitrogen dioxide, while reactive, also penetrates indoors; and an ambient pollution component of

25 total personal exposure to NO_2 can be identified among individuals without indoor NO_2 sources

26 and close to strong outdoor sources such as highways. While there may be some, perhaps many,

27 individuals exposed to elevated concentrations of the gaseous criteria pollutants, in order to

28 contribute to the health effects associated with ambient concentrations of a co-pollutant (e.g,.

29 PM), the ambient gaseous pollutants must be significantly and positively correlated with the

30 exposure to the co-pollutant.

31

1 *8.4.2.2.2 Statistical Issues in the Use of Multi-Pollutant Models*

2   Confounding describes a condition in which one observable potentially explanatory

3 variable in an epidemiological study can stand in for another one, leading to a confusion as to

4 which variable may be causing the outcome. In most PM epidemiology studies, the gaseous

5 pollutants can often stand in for the PM metric because there is frequently a high degree of

6 positive linear correlation among PM metrics and all criteria gaseous pollutants but ozone. This

7 condition, known as multi-collinearity, is necessary to establish confounding, but not sufficient.

8   We will demonstrate these important concepts graphically using causal pathway models.

9 Figure 8-16 shows a model with two pollutants (A and B) whose ambient concentrations and

10 personal exposure are correlated, and both are capable of producing the health outcome. If both

11 A and B exposure concentrations are used in a regression model for the health outcome, and both

12 are in fact causal, then the model is correctly specified. If the personal exposures are available,

13 then estimates of the health effects of both A and B as covariates or regressors will be unbiased,

14 but are likely to have large variances because exposures to A and B are correlated. If only

15 ambient concentrations of A and B are available, then the effect estimates will be biased as well

16 as having large variances, but may still be predictive of health effects for personal exposures to

17 A and B of ambient origin. Disentangling the effects of A and B may be difficult. This

18 corresponds to common notions of confounding.

19

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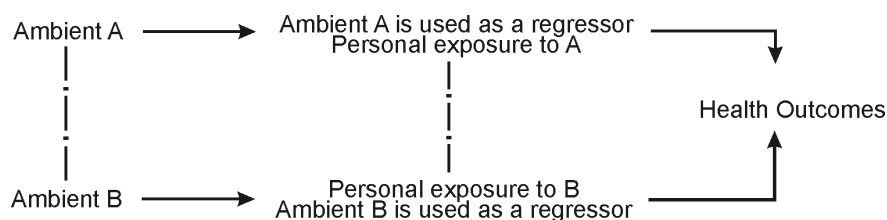
Figure 8-16. Graphical depiction of actual confounding of the effects of ambient A and ambient B.

1   In the figures below, a solid line with an arrow suggests a causal relationship, dot-dash

2 lines suggest a non-direct association, and dotted lines suggest the absence of a pathway, either

3 for exposure or outcome. In principle, it is possible to carry out additional studies to determine

1   whether A and B are both capable of causing independent health effects, although clinical trials

2   with a small number of participants may not have sufficient power to detect and cannot be used

3   to study highly adverse effects (death, hospital admissions) associated with particles or gases at

4   current ambient concentrations and personal exposure levels. Case-crossover study designs may

5   allow larger populations with adverse events to be studied, but are limited by the amount of

6   personal exposure data that can be attributed to the case prior to the occurrence of the adverse

7   outcome. There are a growing number of studies relating ambient concentrations and personal

8   exposures for particles and gases.

9   In Figure 8-16, we assume that both pathways occur in nature, hence a large increase in the

10 standard errors or variances of the effect size estimates in a multi-pollutant study a natural

11 description of confounding. However, variance inflation and effect size instability may also be

12 found in the absence of confounding, as shown in Figures 8-17 through 8-20. In summary,

13 multi-pollutant models may be useful tools for assessing whether the gaseous co-pollutants may

14 be *potential* confounders of PM effects, but cannot determine if in fact they are. Variance

15 inflation and effect size instability can occur in non-confounded models as well as in confounded

16 models. Our usual regression diagnostic tools can only determine whether there is a potential for

17 confounding. Therefore, although multi-colinearity leading to effect size estimate instability and

18 variance inflation are necessary conditions for confounding, they are not sufficient by themselves

19 to determine whether confounding exists.

20

21
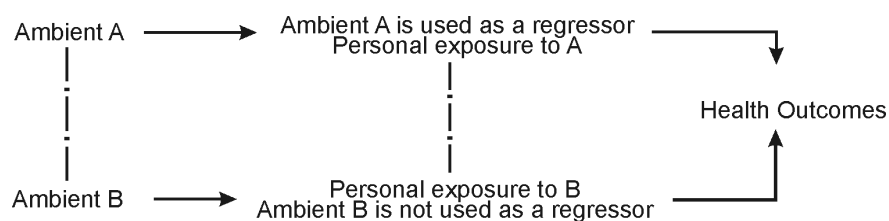
Figure 8-17.   Graphical depiction of under-fitting of A and B.   Only ambient A is used as a regressor (covariate) and B is omitted. The estimate of A's effect is biased because it includes the causal effect of the omitted variable B which is correlated with A.
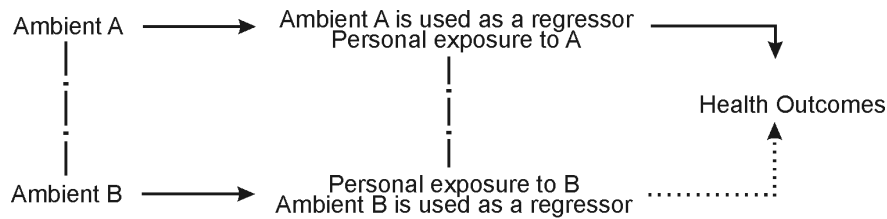
Figure 8-18. Only A is causal, B is not related to the outcome, but both regressors are included in the model, a likely cause of variance inflation.
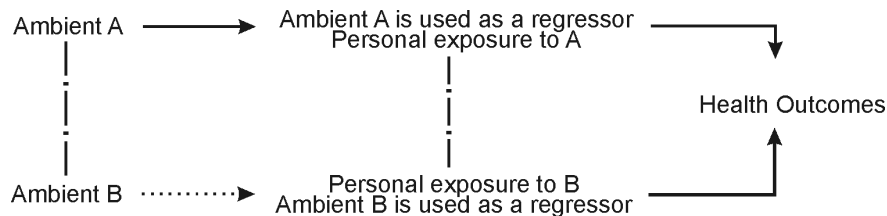
Figure 8-19. Graphical depiction of over-fitting of A and B. Both A and B are causal, and both ambient A and ambient B are used as regressors (covariates). However, there is no relationship of ambient B to personal B. The estimate of A's effect is biased because it includes the hypothetical causal effect of ambient B, which is correlated with A, but for which there is no personal exposure.
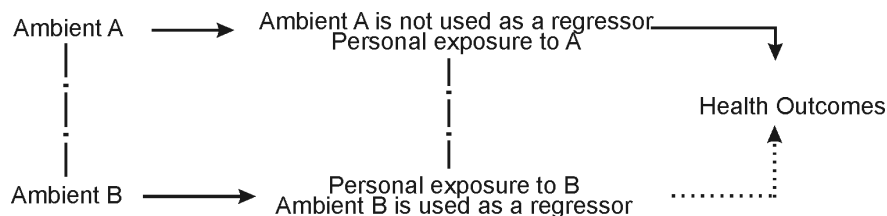
Figure 8-20. Graphical depiction of mis-fitting of the effects of A and B. Only A is causal, B is not related to the outcome, but B is used as a regressor in the model and the effects of A are transferred to B.

1   The most commonly used methods include multi-pollutant models in which both the

2   putative causal agent (PM) and one or more putative co-pollutants are used to estimate the health

3   effect of interest. If the effect size estimate for PM is "stable", then it is often assumed that the

4   effects of confounding are minimal. "Stable" is usually interpreted as meaning that the

5   magnitude of the estimated effect is similar in models with PM alone and in models with PM and

6   one or more co-pollutants, and the statistical significance or width of the confidence interval for

7   the PM effect is similar for all models, with or without co-pollutants. These (usually

8   unquantified) criteria diagnose confounding in a narrow sense, interpreted as synonymous with

9   multi-collinearity, not as a failure of the study design or other forms of model mis-specification.

10   (c) <u>Model mis-specification</u> assumes many forms. The omission of predictive regressors

11   ("underfitting", defined by Chen et al., 2000) may produce biased estimates of the effects of truly

12   predictive regressors that are included in the model. Inclusion of unnecessary or non-predictive

13   regressors along with all truly predictive regressors ("over-fitting") will produce unbiased

14   estimates of effect, but may increase the estimated standard error of the estimated effect if it is

15   correlated with other predictors. Omitting a truly predictive regressor while including a

16   correlated but non-causal variable ("mis-fitting") will attribute the effect of the causal regressor

17   to the non-causal regressor. Interaction terms are candidates for omitted regressor variables. It is

18   important to avoid the "mis-fitting" scenario. Assuming there is a linear relationship when the

19   true concentration-response function is non-linear will produce a biased estimate of the effect

20   size, high or low at different concentrations. One of the most common forms of model mis-

21   specification is to use the wrong set of multi-day lags, which could produce any of the

22   consequences described as "under-fitting" (e.g., using single-day lags when a multi-day or

23   distributed lag model is needed), "over-fitting" (e.g., including a longer span of days than is

24   needed), or "mis-fitting" (e.g., using a limited set of lags while the effects are in fact associated

25   with different set of lags). Different PM metrics and gaseous pollutants may have different lag

26   structures, so that in a multi-pollutant model, forcing both PM and gases to have the same lag

27   structure is likely to yield "mis-fitting". Finally, classical exposure measurement errors (from

28   use of proxy variables) attenuates (biases) effect size estimates under most assumptions about the

29   correlations among the regressors and among their measurement errors (Zeger et al., 2000).

30

31

1   (d) <u>Bias:</u> All of the mis-specifications listed in (c) can bias the effect size estimate except

2   for "over-fitting" and measurement error of Berkson type. The estimates of the standard error of

3   the effect size estimate under "over-fitting" or Berkson error cases are inflated, however.

4   (e) <u>Estimates of effect size standard errors</u> are usually sensitive to model mis-specification.

5   When all truly predictive regressors are added to an "underfit" model, the uncertainty will almost

6   always be reduced sufficiently that the standard errors of estimated effect size are reduced

7   ("variance deflation"). Adding correlated non-causal variables to "over-fitted" or "mis-fitted"

8   models will further increase the estimated standard errors ("variance inflation"). Variance

9   inflation can occur whenever a covariate is highly correlated with the regressor variable that is

10   presumably the surrogate for the exposure of interest. Confounding with the regressor variable

11   can occur only when the covariate is correlated (a) with the regressor variable proxy for the

12   exposure of interest and (b) with the outcome of interest in the absence of the exposure of

13   interest.

14   (f) <u>Mis-specification errors may compound each other</u>. If the concentration-response

15   function is nonlinear but there is measurement error in the exposures, then different sub-

16   populations will have greater or smaller risk than assigned by a linear model. Consider the

17   hypothetical case of a "hockey-stick" model with a threshold. If there were no exposure

18   measurement error, then the part of the population with measured concentrations above the

19   threshold would have excess risk, whereas those below would not. If exposures were measured

20   with error, even if the measured concentration were above the threshold, some people would

21   actually have exposures below the threshold and no excess risk. Conversely, if the measured

22   concentration was below the threshold, some people would actually have concentrations above

23   the threshold and would have excess risk. The flattening of a non-linear concentration-response

24   curve by measurement error is a well known phenomenon that may be detected by standard

25   methods (Cakmak et al., 1999).

26   (g) The question of <u>whether effect size estimates and their standard errors are really</u>

27   <u>significantly different among models</u> is usually not addressed quantitatively. Some authors

28   report various goodness-of-fit criteria such as AIC, BIC, deviance, or over-dispersion index, e.g.,

29   (Chock et al., 2000; Clyde et al., 2000), but the practice is not yet so wide-spread as to assist in

30   analyses of secondary data for use in this document. These models are not strictly nested.

31

1   Variance inflation may also happen with a correctly specified model when both pollutants

2   are causal and highly correlated, compared to a model in which only one pollutant is causal and

3   the non-causal pollutant is omitted. The situation where variance or the standard error decreases

4   when an additional variable is added (variance deflation) suggests that the model with the

5   covariate is more nearly correct and that the standard errors of all covariates may decrease.

6   Statistical significance is a concept of dubious usefulness in assessing or comparing results of

7   many models from the same data set. Still, it is a familiar criterion, and one we address by using

8   a nominal two-sided 5% significance level for all tests and 95% confidence intervals for all

9   estimates, acknowledging their limitations. There is at present no consensus on what clearly

10   constitutes "stability" of a model estimate effect size, e.g., effect sizes that differ by no more than

11   20% (or some other arbitrary number) from the single-pollutant models. Simple comparison of

12   the overlap of the confidence intervals of the models is not used because the model estimates use

13   the same data, and the confidence intervals for effect size in different models are more-or-less

14   correlated. In analyses with missing days of data for different pollutants, comparisons must also

15   incorporate differences in sample size or degrees of freedom. Some examples of (a) changes in

16   the statistical significance of PM effects in different models are evident from inspection of

17   Figures 8-21 to 8-25 and of (b) relative stability in significance of PM effects in Figure 8-26.

18   In any case, statistical comparisons cannot answer questions about either conceptual or

19   statistical issues in confounding with claims about statistical significance. If the model is

20   mis-specified in any of the numerous ways described above, then effect size estimates or their

21   estimated standard errors are biased. Statistical assessments alone can determine if the PM

22   metric is too closely correlated with the other pollutants to provide an accurate quantitative effect

23   size estimate, which is of course useful information even if we conclude that it is not feasible to

24   estimate the separate effects of PM and its gaseous co-pollutants. Confounding cannot occur if

25   the gaseous co-pollutants cannot produce the health outcome, or if there is no personal exposure

26   to the gaseous co-pollutants, or the personal exposure to them is not correlated with their ambient

27   concentrations.

28   We will start by considering what can be learned from the most commonly used approach

29   to diagnose potential confounding, fitting multi-pollutant models and evaluating the stability of

30   the estimated particle effect sizes against inclusion of co-pollutants.

31
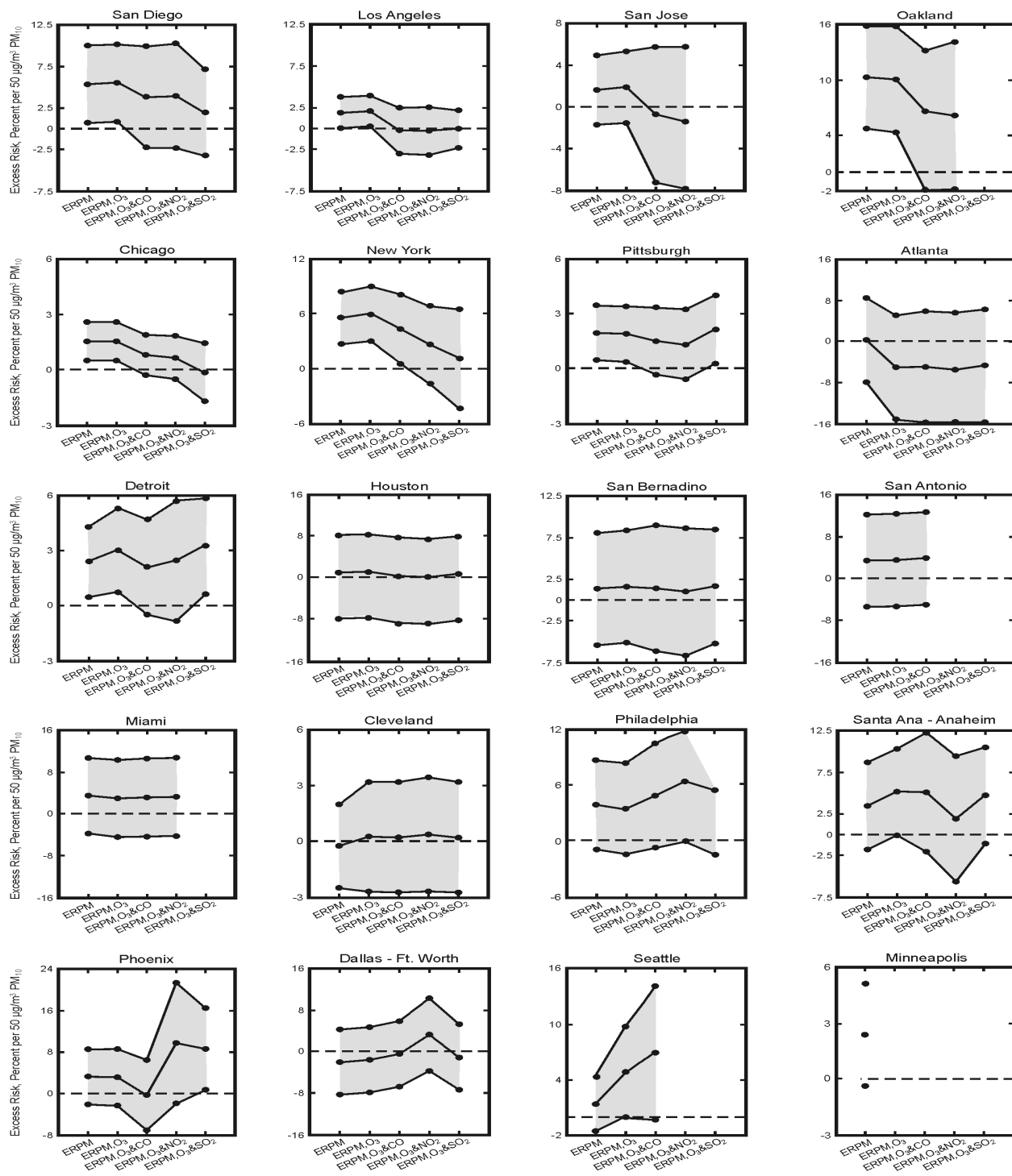
Figure 8-21. Effects of PM$_{10}$ on total mortality in 20 large U.S. cities, as a function of co-pollutant models. EPA presentation of results from Samet et al. (2000b).
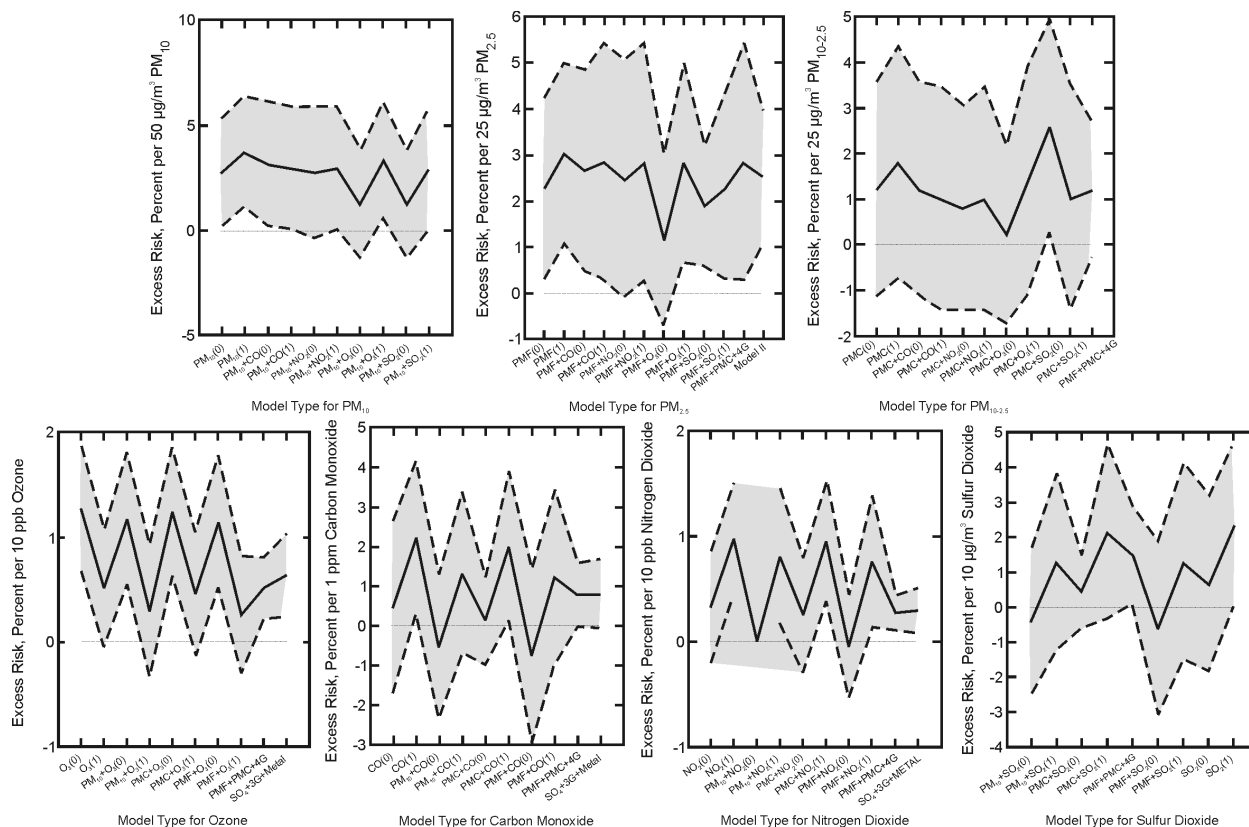
Figure 8-22. Effects of particles and gases on total mortality in eight Canadian cities. EPA presentation of results in Burnett et al. (2000).

1   The studies identified in Table 8-34 are too numerous to allow detailed narrative

2   description here. Rather, Table 8-34 provides a summary emphasizing the points of greatest

3   relevance in evaluating multi-pollutant models. The issue of the stability of the effect size

4   estimate in multi-pollutant models may perhaps be assessed best by reporting the range of effect

5   size estimates across different co-pollutant models, in the absence of quantitative goodness-of-fit

6   comparison criteria in almost all of the papers cited. Thus, in addition to identifying the study,

7   the endpoint (usually total mortality), the PM metric, and the lags used in the analyses, the

8   minimum and maximum effect size estimates and the co-pollutants (if any) for which the

9   estimates were calculated are included. It is not uncommon for the single-pollutant PM model to

10   have the maximum PM effect size, in which case the co-pollutant is listed as "nothing."

11   There is some agreement on what constitutes "variance deflation". If an additional

12   covariate is added to a baseline model (e.g., with PM alone) and the model predicts the outcome
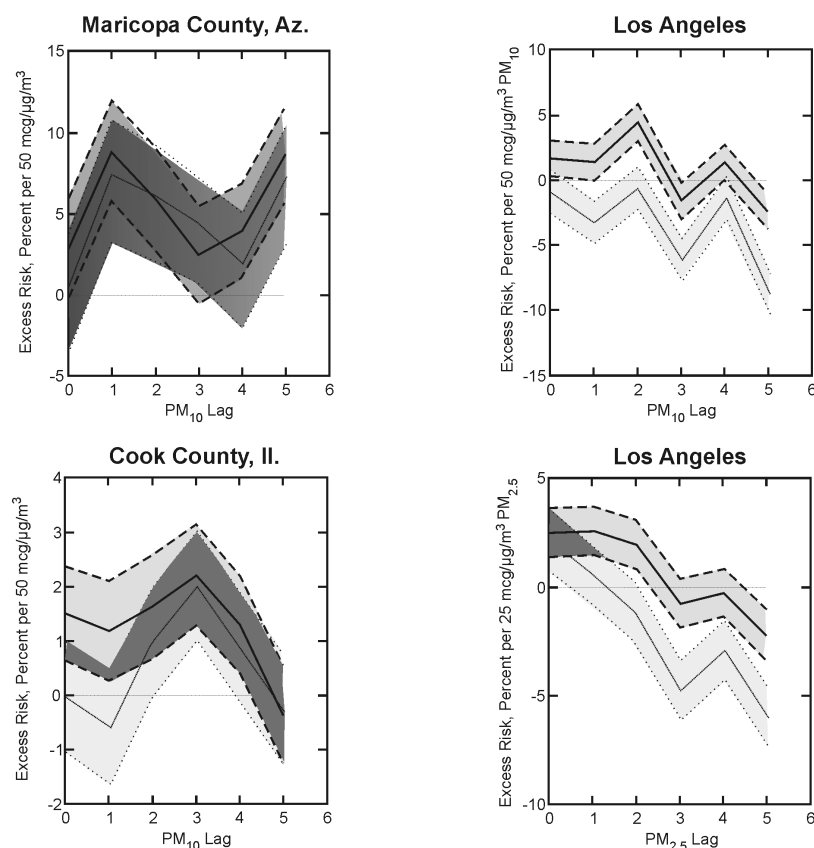
Figure 8-23. **Effects of PM$_{10}$ or PM$_{2.5}$ on circulatory mortality in three U.S. cities as a function of lag days. Dark shading is a co-pollutant model, light shading is a single-pollutant PM model, medium shading shows overlap between single-pollutant and co-pollutant models. EPA presentation of results in Moolgavkar (2000b).**

1 better with the covariate, then the reduction in variance (or deviance for generalized linear or

2 additive models [GLM or GAM]) outweighs the loss of degrees of freedom for variability.

3 Although not always true, it is reasonable to expect a decrease in the estimated asymptotic

4 standard error of the effect size estimate, but improved goodness-of-fit may not reduce the

5 standard errors of all parameters in equal proportion because introducing the new covariate

6 modifies the covariate variance-covariance matrix. The weighted inverse covariance matrix

7 provides an exact estimate for standard errors in ordinary linear regression models, and

8 approximately so in GLM or GAM. The effects on other parameter estimates are rarely reported.

9   "Variance inflation" may occur under several circumstances, including "under-fitting" and

10 "mis-fitting" in which a truly predictive covariate is omitted or replaced by a correlated proxy,
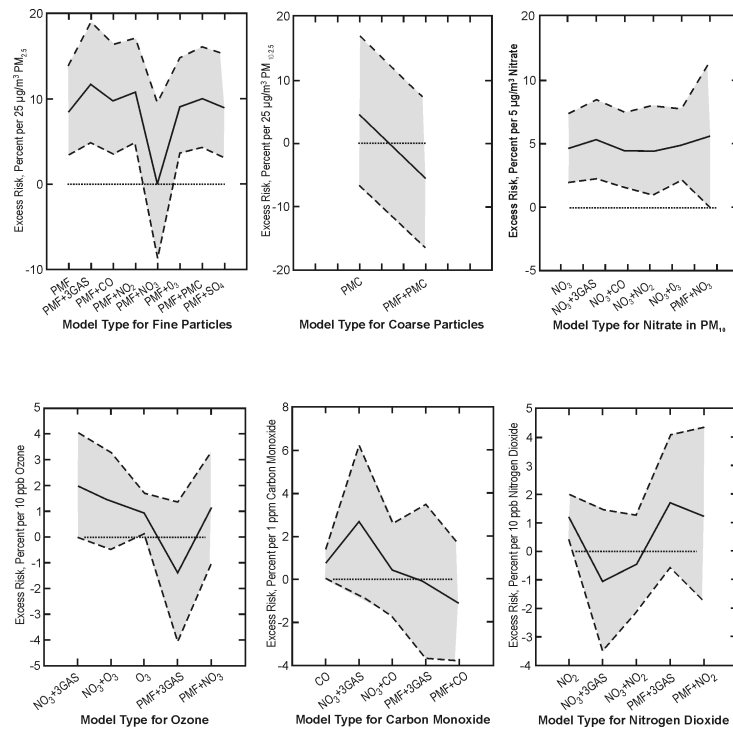
Figure 8-24. Total mortality from particles and gases in Santa Clara County, CA. EPA presentation of results in Fairley (1999).
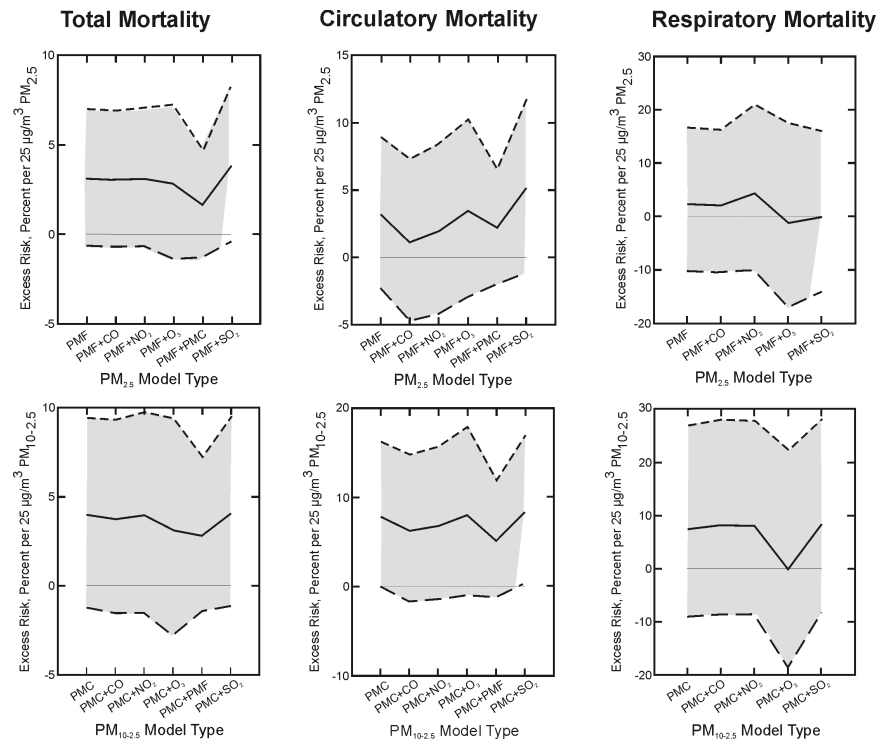
Figure 8-25. Cause-specific fine or coarse particle mortality in Detroit, MI. EPA presentation of results in Lippmann et al. (2000).
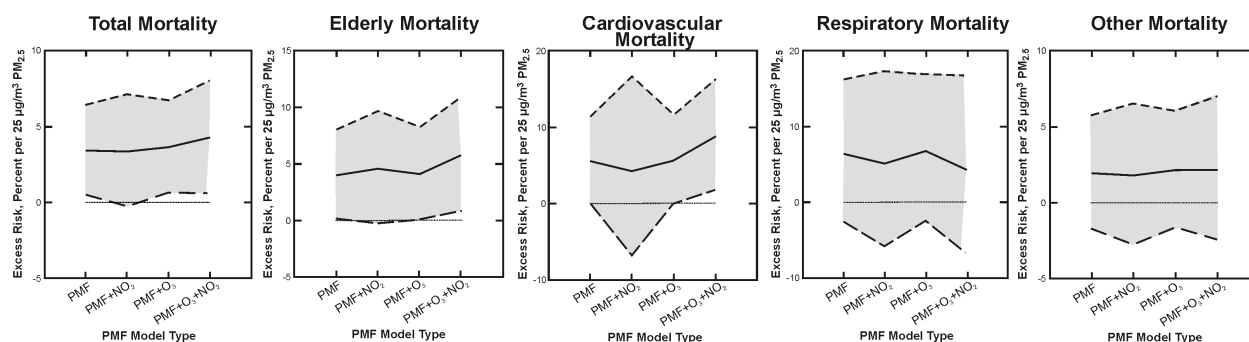
Figure 8-26. Effects of fine particles on total mortality in Mexico City. EPA presentation of results in Borja-Aburo et al. (1998).

1   and "over-fitting" in which a non-predictive covariate correlated with the PM metric is also

2   included in the model. The potential for over-fitting can be diagnosed by evaluating the

3   eigenvalues of the correlation matrix of the predictors, with very small values identifying near-

4   collinearity. However, the complete covariate correlation matrix is almost never reported,

5   including all weather variables and nonlinear functions entered separately as covariates.

6   Nonetheless, even a correlation matrix among all pollutants would be informative. Furthermore,

7   composite correlation matrices in multi-city studies may conceal important differences among

8   the correlation matrices.

9   In the absence of any better criterion, we arbitrarily define "variance deflation" and

10   "variance inflation" as occurring when the estimated standard error of the effect size estimate

11   differs by more than 25% from the single-pollutant models. These are included in Table 8-34 for

12   models for total mortality. Figures 8-21 through 8-26 show results for two multi-city studies, one

13   in the U.S, (Samet et al., 2000b) and one in Canada (Burnett et al., 2000), as well as for some

14   single-city studies in the U.S. and Mexico (Lippmann et al., 2000; Fairley et al., 1999; Borja-

15   Abuto et al., 1999). We do not show other studies because of limitations in space. Readers may

16   form their own judgements about "stability" and "variance inflation/deflation". There are

17   examples of both parameter estimate stability and instability, and of variance inflation and

18   deflation, as noted in Table 8-34.

19

TABLE 8-34. CHARACTERIZATION OF CO-POLLUTANT EFFECTS ON THE STABILITY AND VARIANCE INFLATION OR DEFLATION OF PM EFFECT SIZE ESTIMATE (IN TERMS OF EXCESS RR)

Authors	Year	City	Endpoint	PM Metric	Lag	PM Alone Exc. RR	Age or Season	Min. Exc RR	PM with	Max. Exc RR	PM with	Variance Inflation	Inflation	Inflation	Inflation	Deflation
Samet et al	2000b	Los Angeles	Total Mort.	PM_{10}	1	1.9		−0.3	O_3, NO_2, CO	2.1	O_3	O_3, CO	O_3, NO_2			
Samet et al.	2000b	New York	Total Mort.	PM_{10}	1	5.7		1.1	O_3, SO_2	6.1	O_3	O_3, CO	O_3, NO_2	O_3, SO_2		
Samet et al.	2000b	Chicago	Total Mort.	PM_{10}	1	1.6		−0.2	O_3	1.6	nothing	O_3, SO_2				
Samet et al.	2000b	Dallas-FtW	Total Mort.	PM_{10}	1	−2		−2	nothing	3.4	O_3					
Samet et al.	2000b	Houston	Total Mort.	PM_{10}	1	1		0.1	O_3, NO_2	1.1	O_3					
Samet et al	2000b	San Diego	Total Mort.	PM_{10}	1	5.6		2.1	O_3, SO_2	5.8	O_3	O_3, CO	O_3, NO_2			
Samet et al.	2000b	SantaAna-	Total Mort.	PM_{10}	1	3.5		1.9	O_3, NO_2	5.3	O_3	O_3, CO	O_3, NO_2			
Samet et al.	2000b	Phoenix	Total Mort.	PM_{10}	1	3.3		−0.4	O_3, CO	10.2	O_3, NO_2	O_3, CO	O_3, NO_2	O_3, SO_2		
Samet et al.	2000b	Detroit	Total Mort.	PM_{10}	1	2.4		2.1	O_3, CO	3.3	O_3, SO_2	O_3, CO	O_3, NO_2	O_3, SO_2		
Samet et al.	2000b	Miami	Total Mort.	PM_{10}	1	3.5		3	O_3	3.5	nothing					
Samet et al	2000b	Philadelphia	Total Mort.	PM_{10}	1	3.9		3.5	O_3	6.5	O_3, NO_2	O_3, NO_2	O_3, SO_2			
Samet et al.	2000b	Minneapolis	Total Mort.	PM_{10}	1	2.4		NA	NA	NA	NA					
Samet et al.	2000b	Seattle	Total Mort.	PM_{10}	1	1.4		1.4	nothing	7.4	O_3	O_3	O_3, CO			
Samet et al.	2000b	San Jose	Total Mort.	PM_{10}	1	1.6		−1.4	O_3, NO_2	1.9	O_3	O_3, CO	O_3, NO_2			
Samet et al.	2000b	San Bernard	Total Mort.	PM_{10}	1	1.3		1	O_3, NO_2	1.6	O_3, SO_2					
Samet et al	2000b	Cleveland	Total Mort.	PM_{10}	1	−0.2		−0.2	nothing	0.4	O_3, NO_2, CO	O_3	O_3, CO	O_3, NO_2	O_3, SO_2	
Samet et al.	2000b	Pittsburgh	Total Mort.	PM_{10}	1	2		1.3	O_3, NO_2	2.2	O_3, SO_2	O_3, CO	O_3, NO_2	O_3, SO_2		
Samet et al.	2000b	Oakland	Total Mort.	PM_{10}	1	10.8		5.7	O_3, CO	10.8	nothing	O_3, CO	O_3, NO_2	O_3, SO_2		
Samet et al.	2000b	Atlanta	Total Mort.	PM_{10}	1	0.2		−5.4	O_3, NO_2	0.25	nothing	O_3, CO	O_3, NO_2			
Samet et al.	2000b	San Antonio	Total Mort.	PM_{10}	1	3.5		3.5	nothing	4	O_3, CO					
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	0	2.4		1.9	CO	2.4	nothing	CO				
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	1	2.1		1.9	CO	2.1	nothing	CO				
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	2	1.6		1.6	CO	1.6	either	CO				
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	3	1.1		1	CO	1.1	nothing	CO				
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	4	0.8		0.8	CO	0.8	either	CO				
Moolgavkar	2000b	Chicago	Total Mort.	PM_{10}	5	−0.5		−0.5	nothing	−0.4	CO	CO				
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	0	0.4		−2	CO	0.4	nothing	CO				
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	1	0.9		−4	CO	0.9	nothing					

TABLE 8-34 (cont'd). CHARACTERIZATION OF CO-POLLUTANT EFFECTS ON THE STABILITY AND VARIANCE INFLATION OR DEFLATION OF PM EFFECT SIZE ESTIMATE (IN TERMS OF EXCESS RR)

Authors	Year	City	Endpoint	PM Metric	Lag	PM Alone Exc. RR	Age or Season	Min. Exc RR	PM with	Max. Exc RR	PM with	Variance Inflation	Inflation	Inflation	Inflation	Deflation
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	2	2.4		-1.9	CO	2.4	nothing					
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	3	0.8		-3.9	CO	0.8	nothing					
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	4	0.6		-1.8	CO	0.6	nothing					
Moolgavkar	2000b	Los Angeles	Total Mort.	PM_{10}	5	-2		-5.5	CO	-2	nothing	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	0	2		0.2	CO	2	nothing	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	1	3		0.4	CO	3	nothing	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	2	4.5		0.8	CO	4.5	nothing	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	3	-0.8		-0.8	nothing	-0.8	CO	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	4	0.5		-0.8	CO	0.5	nothing	CO				
Moolgavkar	2000b	Phoenix	Total Mort.	PM_{10}	5	6.1		3	CO	6.1	nothing	CO				
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	0	1.5		0.4	CO	1.5	nothing					CO
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	1	1.4		0.5	CO	1.4	nothing					CO
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	2	0.6		-1.2	CO	0.6	nothing					CO
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	3	-0.6		-1.2	CO	-0.6	nothing					CO
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	4	0.2		-1.1	CO	0.2	nothing					CO
Moolgavkar	2000b	Los Angeles	Total Mort.	$PM_{2.5}$	5	-1.2		-1.5	CO	-1.2	nothing					CO
Fairley	1999	San Jose	Total Mort.	$PM_{2.5}$	0	8.5		-0.1	PM_{10}, nitrate	10.8	NO_2	O_3, CO, NO_2	nitrate			
Fairley	1999	San Jose	Total Mort.	$PM_{10-2.5}$	0	4.5		-5.6	PMF	4.5	nothing					
Fairley	1999	San Jose	Total Mort.	PM_{10}, nitrate	0	4.6		4.4	NO_2	5.6	$PM_{2.5}$	NO_2	$PM_{2.5}$			
Burnett et al.	2000	Canada 8	Total Mort.	$PM_{2.5}$	0	2.3		1.1	O_3	2.6	CO	NO_2				
Burnett et al.	2000	Canada 8	Total Mort.	$PM_{2.5}$	1	3		1.9	four gases	3	nothing	CO	NO_2	O_3, CO, NO_2		Model I
Burnett et al.	2000	Canada 8	Total Mort.	$PM_{10-2.5}$	0	1.2		0.2	O_3	2.6	SO_2					
Burnett et al.	2000	Canada 8	Total Mort.	$PM_{10-2.5}$	1	1.8		1	CO, NO_2, SO_2	1.8	nothing					
Lippmann et al.	2000	Detroit	Total Mort.	$PM_{2.5}$	3	3.1		2.8	O_3	3.9	SO_2					
								1.6	$PM_{10-2.5}$							$PM_{10-2.5}$

TABLE 8-34 (cont'd). CHARACTERIZATION OF CO-POLLUTANT EFFECTS ON THE STABILITY AND VARIANCE INFLATION OR DEFLATION OF PM EFFECT SIZE ESTIMATE (IN TERMS OF EXCESS RR)

Authors	Year	City	Endpoint	PM Metric	Lag	PM Alone Exc. RR	Age or Season	Min. Exc RR	PM with	Max. Exc RR	PM with	Variance Inflation	Inflation	Inflation	Inflation	Deflation
Lippmann et al.	2000	Detroit	Total Mort.	$PM_{10-2.5}$	3	4		3.1	O_3	4.1	SO_2					
								2.8	$PM_{2.5}$							$PM_{2.5}$
Chock et al.	2000	Pittsburgh	Total Mort.	PM_{10}	Tbl.30	3.1	age < 75	2.6	CO	4.3	NO_2	NO_2	CO, SO_2	all 4 gases		
Chock et al.	2000	Pittsburgh	Total Mort.	PM_{10}	Tbl. 90	1.3	age < 75	1.3	nothing	2	all 4 gases					
Chock et al.	2000	Pittsburgh	Total Mort.	PM_{10}	Tbl.6 0	2	age 75+	2	nothing	3.7	CO	NO_2	CO, NO_2	all 4 gases		
Chock et al.	2000	Pittsburgh	Total Mort.	PM_{10}	Tbl. 90	2.2	age 75+	2.2	nothing	2.7	all 4 gases	all 4 gases				
Chock et al.	2000	Pittsburgh	Total Mort.	$PM_{2.5}$	Tbl. 90	2.6	age < 75	2.6	nothing	3.3	all 4 gases					
Chock et al.	2000	Pittsburgh	Total Mort.	$PM_{2.5}$	Tbl. 90	1.5	age 75+	1	all 4 gases	1.5	nothing					
Chock et al.	2000	Pittsburgh	Total Mort.	$PM_{10-2.5}$	Tbl. 90	0.7	age < 75	0.7	nothing	0.8	all 4 gases					
Chock et al.	2000	Pittsburgh	Total Mort.	$PM_{10-2.5}$	Tbl. 90	1.3	age 75+	1.3	nothing	1.4	all 4 gases					
Goldberg et al.	2000a	Montreal	Total Mort.	$PM_{2.5}$ (est)	Mean 0, 1, 2	5.8		5.1	CO	5.9	SO_2					CO (slight)
Goldberg et al.	2000a	Montreal	Total Mort.	$PM_{2.5}$ (est)	Mean 0, 1, 2	with	previous	illness								
		previous	cancer			4.9		4.3	O_3	4.9	nothing					
		previous	acute LRI			12.9		12.8	O_3	13	SO_2					
		previous	airways	disease		3.5		1.6	O_3	3.6	SO_2					
		previous	congestive	heart	failure	10.9		9.4	O_3	10.9	nothing					
	any	previous	coronary	artery	disease	4.9		4.4	O_3	4.9	nothing					
	any	previous	cardio-	vascular	disease	7.4		7.3	O_3	7.4	nothing	O_3	SO_2			
	age 65+	previous	airways	disease	no meds.	11.2		10.5	O_3	11.7	SO_2					
Borja-Abuto	1999	Mexico City	Total Mort.	$PM_{2.5}$	4	3.4		3.4	NO_2	4.2	O_3, NO_2	NO_2	O_3, NO_2			

TABLE 8-34 (cont'd). CHARACTERIZATION OF CO-POLLUTANT EFFECTS ON THE STABILITY AND VARIANCE INFLATION OR DEFLATION OF PM EFFECT SIZE ESTIMATE (IN TERMS OF EXCESS RR)

Authors	Year	City	Endpoint	PM Metric	Lag	PM Alone Exc. RR	Age or Season	Min. Exc RR	PM with	Max. Exc RR	PM with	Variance Inflation	Inflation	Inflation	Inflation	Deflation
Castillejos et al.	2000	Mexico City	Total Mort.	PM_{10}	Avg. 1, 2	9.5		9.5	nothing	13	NO_2	O_3, NO_2				
Castillejos et al.	2000	Mexico City	Total Mort.	$PM_{2.5}$	Avg. 1, 2	3.7		0.4	$PM_{10-2.5}$	3.7	nothing	O_3, NO_2	$PM_{10-2.5}$			
Castillejos et al.	2000	Mexico City	Total Mort.	$PM_{10-2.5}$	Avg. 1, 2	10.5		10.3	$PM_{2.5}$	11	O_3	O_3, NO_2	$PM_{2.5}$			
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{2.5}$	Avg. 1, 2	4.5	summer	2.8	O_3, $PM_{10-2.5}$	4.5	nothing					
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{2.5}$	Avg. 1, 2	1.6	winter	0.8	NO_2	1.8	$PM_{10-2.5}$	$PM_{10-2.5}$	CO	SO_2		
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{2.5}$	Avg. 1, 2	1.8	all year	0.8	NO_2	1.8	nothing	$PM_{10-2.5}$	CO			
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{10-2.5}$	Avg. 1, 2	5.5	summer	3.7	$PM_{10-2.5}$	5.5	nothing					
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{10-2.5}$	Avg. 1, 2	1.8	winter	−0.5	$PM_{10-2.5}$	1.8	nothing	$PM_{10-2.5}$	CO	NO_2		
Cifuentes et al.	2000	Santiago	Total Mort.	$PM_{10-2.5}$	Avg. 1, 2	2.3	all year	0.3	$PM_{10-2.5}$	2.3	nothing	$PM_{10-2.5}$	CO	NO_2		
Atkinson et al.	2000	8 European	Resp. Mort.	PM_{10}		4.6		3.6	SO_2	5.6	NO_2	O_3	SO_2			
Katsouyanni et al.	2001	29 European	Total Mort.	PM_{10}	Avg. 0, 1	3.4		1.8	NO_2	3	SO_2	O_3	NO_2			

Note: Studies with ozone as the only co-pollutant are omitted.

1 **8.4.2.2 Assessments of Confounding Using Multi-Pollutant Models with Observed Gases**

2   The most common approach to evaluation of confounding of PM effects by gaseous

3 co-pollutants is to compare the estimates of the PM effect size in models with and without the

4 gases. The single pollutant model is, in general, of the form

5

6 $$RR = \exp(\beta_{PM} \times PM + \text{other covariates}) \tag{8-1}$$

7

8 and the corresponding multi-pollutant model is of the form

9

10 $$RR = \exp(\beta_{PM} \times PM + \beta_{gas1} \times [gas1] + \beta_{gas2} \times [gas2] + \text{other covariates}) \tag{8-2}$$

11

12 If the estimates of β_{PM} in model specifications in Equations 8-1 and 8-2 are very different, or if its

13 estimated standard error is much larger in Equation 8-2 than in Equation 8-1, then one may

14 conclude that PM is confounded with the gaseous co-pollutants, particularly if PM and the co-

15 pollutants are highly inter-correlated, as they often are. Variance inflation (large standard error)

16 of the estimated β_{PM} in the multi-pollutant model suggests that the pollutants are collinear.

17 A large change in estimated β_{PM} without much variance inflation suggests that some of the total

18 effect might be shared among PM and the gaseous pollutants, whereas a large change in the PM

19 coefficient along with a large increase in the estimated variance of the PM regression coefficient

20 suggests only that the PM coefficient is unstable.

21   The results in Table 8-34 show numerous cases of variance inflation, an expected

22 consequence of the multi-colinearity of PM and gaseous pollutants in most cities where

23 combustion products from motor vehicles, power plants, home heating, and industrial processes

24 dominate the urban air mix. We have not tabulated findings for which the only co-pollutant is

25 ozone (Dominici et al., 2000a; Lipfert et al., 2000; Samet et al., 2000a,c), as these results appear

26 to add little to the findings in (Samet et al., 2000b). Samet et al. (2000b) found that including

27 ozone along with PM_{10} tends to slightly increase the PM_{10} effect, but increasing the variance

28 substantially only in Cleveland and Seattle. Moolgavkar (2000b) finds that adding CO to a PM_{10}

29 model substantially increases its variability at most single-lags in Chicago and Phoenix, but less

30 so in Los Angeles. Adding CO to the $PM_{2.5}$ model in Los Angeles results in a substantial

31 reduction in the uncertainty of the $PM_{2.5}$ effect, one of the few cases of variance deflation,

1   implying a better-fitting model. This suggests that it may be easier to separate the effects of CO

2   from the effects of $PM_{2.5}$ than from the effects of PM_{10} in Los Angeles.

3   Some of the studies in which either PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ coefficients are evaluated in

4   multi-pollutant models are discussed below. A partial list of recent studies for which such

5   assessments can be done is given in Table 8-35. Only a subset of these studies are discussed as

6   examples of what can be learned from multi-pollutant analyses. Table 8-34 presents a summary

7   of the results, ordered starting with studies having clearer indications of PM effect size instability

8   against co-pollutants through to studies having clear indications of PM effect size stability.

9

10   **Samet et al. (2000b) mortality in 20 U.S. cities**

11   Most cities in Samet et al. (2000b) show a considerable reduction in effect size with

12   inclusion of ozone and another pollutant in the model, compared to the model with PM_{10} alone.

13   The maximum PM_{10} effect size across co-pollutant models is rarely much larger than the single-

14   pollutant PM_{10} effect, except in Dallas-Fort Worth, Phoenix, and Seattle. The overall impression

15   in Figure 8-21 is that the co-pollutant models are neither consistently stable nor unstable, so that

16   the sensitivity of the model to co-pollutants may vary substantially from city to city. The results

17   shown are all for a single lag day 1. Results in Moolgavkar (2000b) suggest that different single-

18   day lags in different cities may affect the apparent stability and variance inflation or deflation of

19   the estimated PM effects.

20

21   **Moolgavkar (2000b) total and cardiovascular mortality in 3 U.S. cities.**

22   Results for total mortality are shown in Figures 1, 2, and 3 in the Moolgavkar (2000b)

23   paper, using CO as the only co-pollutant. The assessment of stability and variance

24   inflation/deflation against co-pollutants and lags is shown in Table 8-34 for total mortality where

25   CO is the only co-pollutant, for consistency with Samet et al. (2000b). The results for

26   cardiovascular mortality are shown in Figure 8-23. It is clear that the results depend on both city

27   and lag. The PM_{10} models for total mortality in Los Angeles and Phoenix show systematic

28   attenuation of effect when CO is added, whatever the lag. The PM_{10} effect size in Chicago is

29   only somewhat attenuated by CO. Both Chicago and Phoenix show variance inflation by CO at

30   all lags. In Los Angeles, however, the PM_{10} effect shows little variance inflation by CO except at

31   lags 0 ands 5, even though the PM_{10} effect is strongly attenuated. The $PM_{2.5}$ effect size on total

TABLE 8-35. SOME NEW DAILY TIME SERIES STUDIES FOR MORTALITY OR MORBIDITY WITH CO-POLLUTANT MODELS AND GRAVIMETRIC PM INDICES

Study	City or Cities	PM Indices	Co-Pollutants
Studies in the U.S. and Canada			
Burnett et al. (2000)	8 Canadian Cities	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
Chock et al. (2000)	Pittsburgh, PA	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
Dominici et al. (2000a)	19 U.S. cities with ozone data	PM_{10}	O_3
Fairley et al. (1999)	Santa Clara County, CA	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, COH, NO_3^-, $SO_4^=$	O_3, CO, NO_2
Goldberg et al. (2000, 2001abcd)	Montreal, PQ, Canada	Estimated $PM_{2.5}$, Sutton sulfate, COH	O_3, CO, NO_2, SO_2, NO
Gwynn et al. (2000); Gwynn and Thurston (2001)	Buffalo, NY	$PM_{2.5}$, PM_{10}, COH, SO_4^-, H^+	O_3, CO, NO_2, SO_2
Lipfert et al. (2001)	Philadelphia, PA - Camden, NJ	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3 (only particle co-pollutant)
Lippmann et al. (2000)	Detroit, MI	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
Moolgavkar (2000a)	Los Angeles, CA	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
	Chicago, IL	PM_{10}	O_3, CO, NO_2, SO_2
	Phoenix, AZ	PM_{10}	O_3, CO, NO_2, SO_2
Moolgavkar (2000b)	Los Angeles, CA	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
	Chicago, IL	PM_{10}	O_3, CO, NO_2, SO_2
	Phoenix, AZ	PM_{10}	O_3, CO, NO_2, SO_2
Samet et al. (2000abc)	19 U.S. cities with co-pollutant models	PM_{10}	O_3, CO, NO_2, SO_2
Studies in Latin America			
Borja-Abuto et al. (1998)	Mexico City, D.F., Mexico	$PM_{2.5}$	O_3, NO_2
Castillejos et al. (2000)	Mexico City, D.F., Mexico	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, NO_2
Cifuentes et al. (2000)	Santiago, Chile	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}	O_3, CO, NO_2, SO_2
Loomis et al. (1999)	Mexico City, D.F., Mexico	$PM_{2.5}$	
Studies in Europe			
Atkinson et al. (2001)	8 European cities in APHEA 2	Several, converted to PM_{10}	O_3, CO, NO_2, SO_2
Katsouyanni et al. (2001)	29 European cities	PM_{10}, Black Smoke (BS)	O_3, NO_2, SO_2
Sunyer and Basagna (2001)	Barcelona, Spain	PM_{10}	O_3, CO, NO_2
Studies in Asia			
Kwon et al. (2001)	Seoul, South Korea	PM_{10}	O_3, CO, NO_2, SO_2

1   mortality in Los Angeles is also greatly attenuated, but there is substantial variance deflation.

2   Perhaps CO is either a surrogate or a potential confounder of PM_{10} in Los Angeles.

3

4   **Fairley et al. (1999) total mortality in Santa Clara County (San Jose), CA.**

5   This study is noteworthy because it is, as far as we are aware, the only study using particle

6   nitrates as an exposure index. The PM_{10}-nitrate component is very stable and shows variance

7   inflation from NO_2 and $PM_{2.5}$, as might be expected. The extent to which nitrate is a component

8   of $PM_{2.5}$ rather than PM_{10} in this study is unknown. In many western cities, $PM_{2.5}$ is much more

9   alkaline than in the eastern U.S., so that nitrates are less likely to be displaced to the coarse PM_{10}

10   fraction. In the eastern U.S., where particle acidity is greater, there may be a greater

11   displacement of nitrates from fine particles where sulfates are a much larger fraction of particle

12   mass than in the west, and consequently nitrates are more likely to reside in the coarse fraction in

13   the east. It is therefore uncertain that the nitrate component of the atmosphere can account for

14   the large adverse health effects of PM_{10} observed in many cities in the northeast and industrial

15   midwest. Clearly, it would be desirable to have more epidemiology studies with the nitrate

16   component (size-stratified and measured in a manner to avoid evaporated losses) used as a PM

17   component in models, notwithstanding technical difficulties that might be encountered in

18   measuring the samples. As shown in Table 8-34, the $PM_{2.5}$ effect size estimate is almost

19   eliminated by including PM_{10}-nitrates , and the estimated $PM_{2.5}$ effect size variance inflated by

20   including the criteria gaseous pollutants. As shown in Figure 8-24, the PM_{10}-nitrate and $PM_{2.5}$

21   effect size estimates are stable against gaseous pollutants. It is unlikely that the gaseous

22   pollutants are confounders of PM_{10}-nitrate.

23

24   **Other studies**

25   The results from other studies are also summarized in Table 8-34 and Figures 8-19 to 8-26.

26   There are numerous examples of effect size instability and variance inflation. The only other

27   cases of substantial variance deflation (i.e., better prediction of PM effect size by inclusion of

28   co-pollutants) are in Burnett et al. (2000), Lippmann et al. (2000), and Goldberg et al. (2000a).

29   In Burnett et al. (2000), the model with sulfates as a surrogate for $PM_{2.5}$, three gases, and four

30   metals in $PM_{2.5}$ give a better estimate of the sulfate effect than do the models with the gravimetric

31   $PM_{2.5}$ index. In Lippmann et al. (2000) the models for total mortality with fine or coarse particles

1   give better predictions of the particle effect when the other size component is included than do

2   any of the gaseous co-pollutant models, regardless of the single day lags used for the various PM

3   or gaseous co-pollutants (see Table 8-36).

4

5

TABLE 8-36. SINGLE-DAY LAGS USED IN CO-POLLUTANT MODELS IN
(Lippmann et al., 2000, Tables 13-14)

	Pollutant						
Endpoint	**PM_{10}**	**$PM_{2.5}$**	**$PM_{10-2.5}$**	**O_3**	**CO**	**NO_2**	**SO_2**
Total Mortality	1	3	1	0	1	1	3
Circulatory Mortality	1	1	1	0	1	1	3
Respiratory Mortality	0	0	2	0	1	1	3
Pneumonia Admissions	1	1	1	3	3	3	3
COPD Admissions	3	3	3	3	3	3	3
Ischemic Heart Disease (IHD) Admissions	2	2	2	3	3	3	3
Dysrhythmia Admissions	1	1	0	3	3	3	3
Heart Failure Admissions	0	1	0	3	3	3	3
Stroke Admissions	1	0	1	3	3	3	3

1   **8.4.2.3 Assessment of Confounding in Multi-City Studies: Pooling Effects**

2   One approach to evaluating confounding used in a number of multi-city studies is to pool or

3   combine the results of individual within-city studies using either standard analytic techniques

4   such as inverse variance averaging (Atkinson et al., 2001; Katsouyanni et al., 2001) or Bayesian

5   second-stage meta-analysis methods (Samet et al., 2000a) which may be thought of as another

6   kind of averaging. The argument is that if the pooled or combined PM effect size estimates for

7   the single-pollutant models across a number of cities differing greatly in PM and co-pollutant

8   distributions and correlations are similar to those obtained from PM effect size estimates of

9   multi-pollutant models across the same cities, then it is unlikely that the co-pollutants are

10   confounding the PM effect.

1   The basis of this argument is not self-evident. Examination of the results of Samet et al.

2   (2000a) for the 20 largest U.S. cities discussed in Section 8.2.2.2 shows that there are a variety of

3   different patterns of change in PM_{10} effect size associated with including gaseous co-pollutants in

4   a co-pollutant model. Results for multi-pollutant models in the NMMAPS Part II study (Samet

5   et al., 2000a) for the 20 largest U.S. cities are shown in Section 8.4.2.2, Figure 8-21. The

6   Bayesian posterior distribution of the estimates was shown earlier in Figure 8-3. It should be

7   noted that the posterior distribution for the *mean* PM_{10} effect has about the same standard

8   deviation for all of the co-pollutant models, as might be expected by examining Figure 8-21. The

9   posterior distribution for the mean PM_{10} effect size estimate remains relatively unchanged from

10   the single-pollutant model when O_3 is included as a co-pollutant, and tends to decrease

11   substantially (by about 30%) when either CO or NO_2 are added as co-pollutants in addition to O_3.

12   Adding SO_2 causes a smaller reduction the estimated PM_{10} effect. The estimated PM_{10} effect

13   follows a similar pattern of association with the gaseous criteria pollutants in many large U.S.

14   cities, but shows a very different pattern in other cities, either being stable with respect to co-

15   pollutants or showing increasing effects of PM_{10} with the inclusion of CO, NO_2, or SO_2 in a

16   multi-pollutant model for apparently dissimilar cities including Seattle, WA, Phoenix, AZ,

17   Dallas-Forth Worth, TX, and Philadelphia, PA. One can argue that CO and NO_2 are often

18   closely and positively associated with PM_{10}, especially if PM_{10} is dominated by the fine particle

19   fraction, predominantly from combustion, thus reducing the magnitude and significance of the

20   estimated PM_{10} effect. This explanation is less convincing in cities such as Phoenix, AZ, where

21   excess mortality is better associated with coarse particles than with fine particles (Mar et al.,

22   2000; Smith et al., 2000; Clyde et al., 2000).

23   Moolgavkar (2000b) finds different effects of PM_{10} on circulatory mortality in Phoenix,

24   where the single-pollutant and multi-pollutant models largely agree, disagreeing slightly more in

25   magnitude and significance at lag days 0 and 1, 4 and 5, than at lag days 2 and 3. In general,

26   Moolgavkar finds different temporal patterns of the effect of PM_{10} for single-pollutant and

27   co-pollutant models among Phoenix, AZ, Chicago, IL, and Los Angeles, CA. There are many

28   possible reasons for city-to-city variations in these relationships. One possibility is differences in

29   the mix of fine and coarse particles (which may be quite different in those cities). The combined

30   estimates across cities using the one-day lags for all cities or all regions may overlook different

1 delays associated with different causes for total or cause-specific mortality in different cities,

2 suggesting that caution be used when pooling data from different places.

3   Analogous differences in the stability of the estimated PM coefficients have also been

4 noted in other city-specific studies discussed in Section 8.4.2.2. Does the occasional instability

5 of PM coefficients in co-pollutant models across different cities reflect real differences, or is it

6 merely another kind of statistical variability that might be explained in a second-stage

7 regression? Second-stage regression approaches are discussed next in Section 8.4.2.4.

8

9 **8.4.2.4 Assessment of Confounding in Multi-City Studies: Regression**

10 *8.4.2.4.1 Second-Stage Regression and Identification of Effects Modifiers*

11   The approach used by Atkinson et al. (2001); Janssen et al. (2002); Katsouyanni et al.

12 (2001); Levy et al. (2000); and Samet et al. (2000b) is to accept the estimated PM effect-size

13 estimates as samples from a distribution of possible effect sizes in different cities (a "meta-

14 population") and to fit a weighted regression model of the estimated effect sizes on various

15 community-wide indices. The community-wide indices for these studies have included: (a) the

16 mean or median levels of co-pollutants; (b) the median or trimmed mean of the correlations of

17 the PM_{10} concentrations at different sites across the city (as an index of spatial measurement

18 error); (c) characteristics of particles such as the observed or estimated $PM_{2.5}/PM_{10}$ ratio;

19 (d) some characteristics of the distribution of meteorological variables (e.g., mean maximum

20 annual temperature); (e) some community-wide surrogates for possible sources (e.g., density of

21 vehicle miles traveled, percent of population using public transportation, or $PM_{2.5}/NO_2$ ratio as

22 indicators of motor vehicle use); (f) factors possibly affecting exposure (e.g., percentage of

23 residences with air conditioning); and (g) sociodemographic characteristics possibly affecting

24 exposure and susceptibility to particles (e.g., average education level, percentage of residents

25 >64 years of age, measures of immigration or emigration from the community).

26   Samet et al. (2000b) found that estimated PM_{10} effects on total mortality (a) increased with

27 increasing mean O_3 (not significant in any model), increasing mean NO_2 (significant in three- and

28 four-variable models, only marginally significant in a five-variable model), and increasing

29 percentage without a high school diploma, but (b) decreased with increasing mean PM_{10}

30 (significant only in the best five-pollutant model) and the median PM_{10} cross correlation.

1   Janssen et al. (2002) found variations among PM_{10} effects on hospital admissions in single-

2   pollutant models to be associated with differences in: the community-wide prevalence of air

3   conditioners; sources of PM_{10}, population density; and density of vehicle traffic (mean daily

4   vehicle miles of urban travel per square mile). The same 14 cities used in the hospital

5   admissions studies in Samet et al. (2000b) were divided into two groups, five in which PM_{10}

6   concentrations peaked in the winter (Boulder and Colorado Springs, CO; Provo-Orem, UT;

7   Seattle and Spokane, WA) and nine others where PM_{10} concentrations peaked in the summer

8   (Birmingham, AL; Canton and Youngstown, OH; Chicago, IL; Detroit, MI; Minneapolis, MN;

9   Nashville, TN; New Haven, CT; Pittsburgh, PA). There was a statistically significant negative

10   relationship between the percentage of homes with central air conditioning and the regression

11   coefficient (excess relative risk) for cardiovascular disease, this being lower in winter-peaking

12   cities than in summer-peaking cities. The relationship between exposure and ventilation rate is

13   discussed further in Section 8.4.2.5. Ventilation rate also effects personal exposure to gaseous

14   co-pollutants. Additional studies similar to Jannsen et al. (2002) would likely help clarify further

15   the associations between particles and gases and may offer a useful alternative method for

16   assessing multi-pollutant models across different cities.

17   Katsouyanni et al. (2001) found that PM_{10} effects on mortality increased with mean NO_2

18   level, mean temperature, and percentage of population with age > 65 years. The estimated PM_{10}

19   effects decreased with increasing PM_{10}/NO_2 ratio, increasing relative humidity, and increasing

20   age-adjusted mean mortality rate in the 29 cities in the APHEA II study in Europe.

21   Atkinson et al. (2001) studied respiratory mortality in eight European cities and found a

22   significant positive relationship between asthma mortality at ages 0 to 14 years and the percent of

23   population > age 65, a significant negative relationship with community smoking prevalence, and

24   a negative relationship with relative humidity. In the analyses for age 65+ total respiratory

25   mortality, and age 65+ mortality from asthma and COPD, effect size increased significantly with

26   larger mean O_3.

27   These studies, while quite informative, do not address the core issue in assessment of

28   potential confounders: in any single city, it is often difficult to disentangle the components of the

29   mixture of air pollutants that actually exists. The problem derives from the typically co-linear

30   relationship of particles and gaseous co-pollutants, where co-pollutants may have relatively high

31   linear correlation coefficients among themselves. The assessment of confounding depends on the

1	correlations among the pollutants, not on their absolute levels. It would be possible for
2	co-pollutants to have exactly the same correlations with PM even if the absolute concentrations
3	of the co-pollutants differed greatly from one city to the next. For this reason, even if the
4	co-pollutant concentrations are very low, co-linearity could still be manifested in a
5	multi-pollutant model because the co-pollutant would increase and decrease in step with the PM
6	index due to common meteorological conditions. For example, in a recent study of respiratory
7	symptoms in Port Alberni, BC, Canada, the levels of SO_2 and other pollutants are low, and are
8	less likely to be the cause of the observed effects (so not a confounder), but may complicate a
9	multi-pollutant model because of their co-linearity with PM.
10	Another issue is whether the mean or median PM or co-pollutant concentration is the best
11	covariate in a second-stage model. An indicator of high-level concentrations might be
12	informative, e.g., the mean or median of 95th percentiles for each year (approximately the 3rd
13	largest of 61 annual every-6th-day observations for PM and the 18th largest for 365 daily measures
14	of the co-pollutants).
15	

8.4.2.4.2 Regression of Effect Size Coefficients on Co-Pollutant vs. PM Coefficients in a Multi-City Study

18	Several authors (Samet et al., 2000b; Schwartz, 1999, 2000a) have applied two-stage
19	regression techniques in an effort to identify the extent to which a pollutant is directly associated
20	with human health effects, as opposed to acting indirectly through its association with other
21	pollutants. Noting that relationships between co-pollutants differ by city, it has been proposed
22	that such differences can facilitate the separation of direct and indirect effects through use of a
23	second-stage meta-regression. The second-stage meta-regression approach regresses the city-
24	specific PM regression coefficients (which may have been adjusted for individual-level or time-
25	varying covariates in a previous stage) against the city-specific correlations between PM and a
26	selected co-pollutant. Typically the second-stage regression model is limited to a single
27	independent variable, and the regression results are presented graphically along with the data
28	points. For the results of the second-stage regression, a non-zero slope is taken as evidence of
29	confounding by the co-pollutant, while a non-zero intercept is taken as evidence of a true,
30	unconfounded association with PM.
31	Marcus and Kegler (2001) demonstrate that the use of the intercept as an indicator an
32	unconfounded association will only work if the second-stage model has been correctly specified.

1   Their counter-example is simply the case where the PM association is independently confounded

2   by two co-pollutants and only one of these confounders is included in the second-stage regression

3   model. In this case, the PM association would still be confounded by the omitted co-pollutant

4   and a non-zero intercept from the mis-specified model would not be valid evidence of an

5   unconfounded association with PM.

6   The counter-example is an illustration of residual confounding which is already well-

7   understood by epidemiologists. Residual confounding may arise (1) when a regression model

8   fails to include all of the potential confounders or (2) when a regression model includes a poorly

9   measured covariate that captures only a portion of the confounding by that covariate. The

10   approach to the evaluation of confounding proposed by Schwartz and Samet et al. could be

11   improved by the simple expedient of use of a multi-variate second-stage regression, in which the

12   model includes several gaseous co-pollutants. Even a multi-variate model would not fully

13   resolve the issue of residual confounding in the case of (a) poorly measured covariates or (b)

14   other omitted covariates. In either of these cases, the use of a non-zero intercept as evidence of a

15   true, unconfounded association with PM would be incorrect.

16   However, the most important aspect of the approach proposed by Schwartz and Samet et al.

17   was not their use of the intercept, but rather their use of the second-stage slope as an indication of

18   both the presence and magnitude of confounding by the modeled co-pollutant. The simulations

19   illustrated in the article by Marcus and Kegler clearly demonstrate that a confounding

20   co-pollutant would produce a non-zero slope, even in the presence of omitted confounders.

21   In addition to confounding, a non-zero slope might, under certain circumstances, also be

22   evidence of effect modification of a true PM association by the modeled co-pollutant.

23   Conversely, the absence of a slope in the second-stage regression could be evidence that the

24   particulate matter association is neither confounded nor modified by the modeled co-pollutant, or

25   that positive slopes could be obscured by negative slopes in relationships among co-pollutants,

26   suggested by the observation that the longitudinal correlations between PM_{10} and O_3 or between

27   NO_2 and O_3 are often negative.

28

29

30

8.4.2.5 Assessment of Confounding Based on Exposure

8.4.2.5.1 Review of Sarnat et al. (2001): Is there significant personal exposure to gaseous co-pollutants?

A direct method for evaluating whether a putative causal factor is confounded by another factor is based on the requirements that a confounder be (1) associated with the health outcome or disease, and (2) associated with exposure to the putative causal factor. If individuals are not exposed to a potential confounder, then it cannot be a confounder of another agent to which the individual is exposed, although there is no guarantee that the putative causal factor causes the outcome unless there is evidence of biological effects at the levels to which the individual is exposed. The most likely potential confounders in air pollution epidemiology studies are the gaseous criteria pollutants, specific size components or chemical components of particles, and meteorological variables associated with exposure to PM or other pollutants. Many of these potential confounding factors have been shown to cause adverse cardiovascular or respiratory effects after exposure to elevated levels in laboratory animal studies, in *in vitro* experimental studies, or as small physiological or functional changes in human adult volunteers. There is also evidence for toxic effects from either short-term or long-term exposures to other ambient air pollutants with which the criteria pollutants are associated. Finally, while extremes of temperature and humidity are known to be independently associated with increases in mortality and morbidity, they are also associated with concentrations and possibly even exposures (e.g., by closing the windows and using air conditioners) to these pollutants, as well as ambient particles. Thus, the gaseous co-pollutants and other environmental variables cannot be totally precluded as confounders on the basis of lack of effects independent of PM.

The question raised in two important papers by Sarnat et al. (2000, 2001) addresses the exposure aspect of confounding, i.e., are the gaseous pollutants confounders or surrogates of PM effects? The first study (Sarnat et al., 2000) enrolled 15 non-smoking elderly participants (age 65+, average 75 years) in Baltimore, MD, who wore multi-pollutant personal samplers during the summer of 1998 and the winter of 1999. Selection of participants was non-random, as they all were healthy (i.e., asymptomatic) non-smokers, living in private residences, all with central air conditioning but one (denoted SA4). The participants came from a range of socio-economic backgrounds and locations within Baltimore (details not reported). The ambient pollutant concentrations were measured at seven state or federal monitoring sites (shown in Chang et al., 2000, Figure 2), five in the city of Baltimore and two in suburban counties, all within nine miles

1   of the central business district site denoted CBD1. Longitudinal within-subject correlations of

2   personal and ambient $PM_{2.5}$ were high in the summer (median Spearman r = 0.74) and low in the

3   winter (median r = 0.25), and residential ventilation was an important determinant of this

4   association (high in well-ventilated environments, low in poorly-ventilated environments). The

5   highest association, on average, was between personal and ambient $SO_4^=$, given that $SO_4^=$ has few

6   indoor sources. There were successively smaller mean correlations between personal and

7   ambient concentrations for $PM_{2.5}$, PM_{10}, O_3, NO_2, and $PM_{10-2.5}$ in the summer, and PM_{10}, $PM_{2.5}$,

8    $PM_{10-2.5}$, O_3, NO_2, SO_2 in the winter, as shown in Table 3-6 of Sarnat et al. (2000). The lower

9   correlations between personal and ambient concentrations of the gaseous pollutants may reflect

10   both the much greater spatial heterogeneity of the gaseous pollutants (except possibly for ozone),

11   and the fact that many gaseous pollutant concentrations were below the seasonal detection limit

12   in Baltimore, producing negative median concentrations for some participants.

13   The study design should be considered in some detail. Each study period was divided into

14   three 12-day segments (denoted A, B, C) , with participants providing n = 9 to 12 days of

15   personal exposure data from which the longitudinal correlation coefficients for each participant

16   were calculated. The participants in each successive 12-day block or group were different

17   individuals with different residence locations, possible patterns of behavior, and household

18   characteristics that may have affected exposure. The number of participants (N) in each block is

19   shown in Table 8-37. One might hypothesize no difference among blocks in this small sample.

20   The results presented in Sarnat et al. (2000) have been aggregated over these three waves or

21   blocks. In spite of the admittedly very small numbers, one might ask whether the aggregation or

22   pooling across blocks is appropriate, given that the participants in each block are independent of

23   each other. The evaluate this, we transformed the correlation data to more nearly normally

24   distributed observations with constant variance, as if the Spearman correlation coefficient r was a

25   Pearson coefficient, using the Fisher Z-transformation, $Z = 0.5 (\ln(1 + r) - \ln(1 - r))$. We then

26   tested the hypothesis that the mean values of the transformed personal to ambient correlations

27   were the same in blocks A, B, C on average, using a standard analysis of variance test.

28   There were no significant differences among the correlation between summertime personal

29   exposure and ambient air pollution among blocks A, B, C for pollutants that are believed to have

30   a reasonably uniform spatial distribution in summer, including $SO_4^=$, $PM_{2.5}$, PM_{10}, and O_3. The

31   $PM_{10-2.5}$ difference is also very non-significant if SC5 is included in the data, but becomes

**TABLE 8-37. NUMBER OF PARTICIPANTS, N, IN EACH BLOCK FOR THE
EXPOSURE STUDY IN SARNAT ET AL. (2000)**

Block	Approximate Dates	Number N
	Summer 1998	
A	June 3 0 - July 12	3
B	July 14 - July 25	6
C	July 27 - August 7	5
Total	June 30 - August 7	14[*]
	Winter 1999	
A	February 2 - February 13	4
B	February 16 - February 27	4
C	March 2 - March 13	6
Total	February 2 - March 13	14[*]

[*]One of the 15 participants was excluded because of high exposure to environmental tobacco smoke outside
the residence.

1 statistically significant when $PM_{10-2.5}$ from this participant is excluded. Differences among the

2 correlation between summertime personal exposure and ambient NO_2 among blocks A, B, C is

3 nearly significant, even though there is a larger within-block variance for the other pollutants,

4 consistent with NO_2 having a somewhat non-uniform spatial distribution.

5   We note significant between-block differences among the correlation between wintertime

6 personal exposure and ambient air pollution among blocks A, B, C for pollutants that had a

7 reasonably uniform spatial distribution in summer, including $SO_4^=$ and PM_{10} in spite of the small

8 numbers and large within-block variance of personal correlations. There was also greater

9 evidence for between-block differences in the wintertime correlation between total personal

10 exposure and ambient $PM_{2.5}$ concentration (P = 0.11 for Z) than for the summertime correlation

11 (P = 0.24). There was little indication of wintertime temporal variability among the personal-

12 ambient correlations for NO_2, SO_2, and O_3, the ambient concentrations of which were often

13 below the wintertime detection limit. The $PM_{10-2.5}$ interblock difference in person al vs. ambient

14 correlation is also very non-significant. We believe it is useful to recognize that large differences

1   among people and temporal blocks of personal-ambient correlation coefficients for gases and

2   particles may require personal exposure studies with a sufficient number of participants and of

3   longer duration to establish those relationships with a high degree of statistical certainty. This

4   analysis would be meaningful only if one block was high and significant and another was low

5   and insignificant.

6   The correlation of personal $PM_{2.5}$ exposure to ambient concentrations of other pollutants

7   was also reported in Table 7 of Sarnat et al. (2000). The median correlation of personal $PM_{2.5}$

8   exposure with ambient $PM_{2.5}$ was higher than the correlation of personal exposure to $PM_{2.5}$ with

9   any of the ambient concentrations of $PM_{10-2.5}$, O_3, NO_2 in summer, but actually smaller in winter

10   with $PM_{10-2.5}$ and NO_2. The correlation of winter $PM_{2.5}$ exposure and ambient O_3 is very negative.

11   It would also have been useful to have ambient measurements at locations near the

12   participants' residences, in order to determine whether the difference in strength of association is

13   related to the heterogeneity in the spatial and temporal distribution of co-pollutant gases and

14   coarse particles relative to central site monitors versus the comparative (but not absolute)

15   homogeneity of $PM_{2.5}$ measurements, a "measurement error" problem reviewed in

16   Sections 8.4.5.3 and 8.4.7.2. Finally, it would have also been desirable to have reported the

17   correlations between personal exposure to each of the gaseous co-pollutants versus the ambient

18   concentration of $PM_{2.5}$ for each participant, analogous to Table 6. This would have allowed a

19   more direct comparison of the hypothesis in Sarnat et al. (2001) reviewed next in

20   Section 8.4.2.5.2.

21

22   *8.4.2.5.2 Review of Sarnat et al. (2001): Are gaseous pollutants confounders or surrogates?*

23   The Sarnat et al. (2001) paper extends the results in Sarnat et al. (2000) to additional

24   cohorts and participants: (a) 21 healthy children, ages 9 to 13 years; (b) 15 individuals with

25   COPD, average age 65 years; and (c) a total of 20 older healthy adults of average age 75 years,

26   6 more than in the earlier paper. All participants were non-smokers who lived nonsmoking

27   private residences. Fourteen of the healthy adults participated in both summer and winter

28   sampling campaigns described above. The COPD cohort consisted of individuals with

29   physician-diagnosed COPD, with an average age younger than the healthy adult cohort. The

30   sampling plan is shown in Table 1 of Sarnat et al. (2001). Although the participants lived in

1   various parts of Baltimore city and County and had a range of socio-economic backgrounds, they

2   were not selected as a representative sample of susceptible sub-populations.

3   The Sarnat et al. publication reports on personal monitoring of 56 subjects for fine PM, O_3,

4   NO_2, and SO_2 in comparison with ambient concentrations of these substances. For fine PM, the

5   personal measurements are associated with the ambient fine PM central-site measurements, O_3

6   (negative in winter), NO_2, CO (winter only), and SO_2 (winter only and negative). For the gaseous

7   co-pollutants, the various personal measurements are not positively associated with the ambient

8   central-site measurements of the same gas. The authors conclude that the ambient, central-site

9   measurements of the gaseous co-pollutants may be surrogates for specific constituents of fine PM

10   rather than confounders.

11   Among the combined sample of 56 participants, the highest median correlation between

12   personal exposure and ambient concentration was for particle sulfates, a component of

13   predominately ambient origin. Sulfates had a summertime median Spearman correlation of 0.88,

14   13 correlations being significant out of 14 for older healthy adults, and a wintertime median

15   correlation of 0.71, 16 out of 29 being significant correlations including 14 healthy adults. The

16   median Spearman correlation between total personal exposure and ambient concentration was

17   also high for $PM_{2.5}$, with a median Spearman correlation of 0.65, 13 significant correlations

18   among 24 healthy older adults and children combined, and a wintertime median correlation of

19   0.22, with 10 of 44 significant correlations using data combined from the three cohorts. Among

20   the gaseous co-pollutants, the personal-ambient correlation was highest for NO_2, with 7 out of

21   44 significant correlations using data combined from the three cohorts.

22   The ambient pollutants are correlated as expected, with high positive summertime

23   correlations seen between the regionally more correlated pollutants $PM_{2.5}$ and O_3, between two

24   combustion products NO_2 and CO, and a positive significant correlation between ambient $PM_{2.5}$

25   and NO_2 shown in Table 8-38. There are high *negative* wintertime correlations between the

26   regionally correlated pollutant O_3 and the combustion products $PM_{2.5}$, NO_2, or CO, and high

27   positive correlations among the combustion products $PM_{2.5}$, NO_2, and CO.

28   Total personal exposure to $PM_{2.5}$ and exposure to estimated ambient $PM_{2.5}$ is not

29   significantly correlated with personal exposure to gases, except for NO_2 exposure in summer.

30   Sarnat et al. (2001) expressed this as a linear regression, with personal $PM_{2.5}$ the dependent

31   variable and personal exposure to NO_2, O_3, or SO_2 as the independent variable, finding that:

TABLE 8-38. CORRELATIONS AMONG AMBIENT POLLUTANTS IN BALTIMORE. SUMMERTIME CORRELATIONS IN UPPER RIGHT, WINTERTIME IN LOWER LEFT. STATISTICALLY SIGNIFICANT SPEARMAN'S CORRELATIONS ARE SHOWN AS UNDERLINED BOLD VALUES.

Pollutant	$PM_{2.5}$	O_3	NO_2	CO	SO_2
$PM_{2.5}$	1	**0.67**	**0.37**	0.15	—
O_3	**−0.72**	1	0.02	−0.06	—
NO_2	**0.75**	**−0.71**	1	**0.75**	—
CO	**0.69**	**−0.67**	**0.76**	1	—
SO_2	−0.17	**0.41**	**−0.17**	−0.12	1

Source: Based on Table 3 in Sarnat et al. (2001).

1   (Personal exposure to $PM_{2.5}$) = **18.65** + **0.18** (Personal exposure to NO_2)   (8-4)

2

3   in summer, with both slope and intercept terms statistically significant and NO_2 measured in

4   units of parts per billion (ppb). It is likely that the relative measurement error of $PM_{2.5}$ exposure

5   is smaller—possibly much smaller – than that of personal exposure to the gaseous pollutants, as

6   shown from Tables 1, 4, and 5 in Sarnat et al. (2000). Among the 14 healthy older adults in the

7   earlier study, only 3 had mean summer exposure concentrations for O_3 greater than the

8   summertime limit of detection (LOD) of 6.6 ppb (SC2, SC4, SC5, all in block C), only 3/14 of

9   the mean NO_2 personal exposures below the LOD (SA1, SA2, SB3) of 5.5 ppb, but all of the

10   mean $PM_{2.5}$ exposure concentrations were 5 to 12 times larger than the summertime LOD of 2.6.

11   None of the wintertime mean O_3 exposure concentrations is larger than the LOD, and 5 of the

12   6 mean O_3 exposures in block C are negative. Only 2 of 14 wintertime mean NO_2 exposures is

13   smaller than the LOD (WA1, WB1) of 11.7 ppb, whereas all of the $PM_{2.5}$ personal exposures

14   means are above the LOD, some by a factor of 12 to 13.

15   Figure 2 in Sarnat et al. (2001) shows box plots of the distribution of Spearman correlations

16   between personal and ambient concentrations for individual participants. In the summer, the

17   median correlation between personal O_3 and ambient O_3 is quite low (left-hand box) and only one

18   correlation is statistically significant, much lower than the median correlation between personal

1   O_3 and ambient $PM_{2.5}$ (right-hand box) where five correlations are statistically significant.

2   However, while the summertime median correlation between personal NO_2 and ambient NO_2 is

3   also quite low (left-hand bar) and only three correlations are statistically significant, it is not

4   much lower than the median correlation between personal NO_2 and ambient $PM_{2.5}$ for which four

5   correlations are significant. The median correlations are, of course, much higher for ambient

6     $PM_{2.5}$ vs. ambient O_3 or NO_2. Thus, ambient $PM_{2.5}$ may be a better proxy for personal exposure

7   to O_3 than is ambient O_3. However, personal exposure to NO_2 is almost as well correlated with

8   ambient NO_2 as with ambient $PM_{2.5}$. If it is believed that exposure to NO_2 also causes adverse

9   health effects, along with exposure to $PM_{2.5}$, then it is not clear that ambient $PM_{2.5}$ is merely a

10   proxy for ambient NO_2.

11   In the winter, the median correlation between personal O_3 and ambient O_3 is quite low

12   (left-hand box) and no correlations are statistically significant, whereas the wintertime median

13   correlation between personal O_3 and ambient $PM_{2.5}$ (right-hand box) where seven correlations are

14   statistically significant and negative. While the wintertime median correlation between personal

15   NO_2 and ambient NO_2 is also quite low (left-hand bar), six correlations are positive and

16   statistically significant, the median personal-ambient NO_2 correlation is not much lower than the

17   median correlation between personal NO_2 and ambient $PM_{2.5}$ for which four correlations are

18   significant. The median correlations are, of course, much higher for ambient $PM_{2.5}$ vs. ambient

19   O_3 or NO_2. Thus, ambient $PM_{2.5}$ may be a better proxy for personal exposure to O_3 than is

20   ambient O_3. However, personal exposure to NO_2 is about as well correlated with ambient NO_2 as

21   with ambient $PM_{2.5}$. If it is believed that exposure to NO_2 also causes adverse health effects,

22   along with exposure to $PM_{2.5}$, then it is not clear that ambient $PM_{2.5}$ is merely a proxy for ambient

23   NO_2. Wintertime personal exposure to SO_2 tends to be negatively associated with both ambient

24   SO_2 and ambient $PM_{2.5}$, with similar median correlations, but with one significantly negative

25   correlation against ambient SO_2 vs. four significantly negative correlations against ambient

26    $PM_{2.5}$. Thus, ambient $PM_{2.5}$ may be a surrogate for personal SO_2 exposure.

27   CO personal exposures have little correlation with ambient $PM_{2.5}$ in summer, with only two

28   statistically significant correlations, but may be more strongly associated with ambient $PM_{2.5}$ in

29   winter, showing five positive and one negative significant correlation and a larger positive

30   median correlation. However, there is no distribution of correlations of personal vs. ambient CO

31   with which to compare these findings.

1   Personal exposures to O_3 are more positively correlated with personal exposures to $PM_{2.5}$ in

2   summertime, and more negatively correlated in wintertime, than are personal O_3 exposures with

3   ambient O_3, and the associations of personal O_3 with ambient $PM_{2.5}$ even more so, suggesting that

4   ambient $PM_{2.5}$ may be a good surrogate for personal O_3. On the other hand, summertime

5   personal NO_2 is no more closely associated with personal $PM_{2.5}$ than with ambient NO_2, and only

6   slightly less so than with ambient $PM_{2.5}$, so that even if personal $PM_{2.5}$ measurements were

7   available, one would expect them to be no more informative about NO_2 personal exposures than

8   would ambient NO_2. Wintertime personal NO_2 is not associated with personal $PM_{2.5}$, and about

9   equally associated with ambient NO_2 and with ambient $PM_{2.5}$, so that even if personal $PM_{2.5}$

10   measurements were available, one would expect them to be completely uninformative about NO_2

11   personal exposures compared to ambient NO_2.

12   Table 9 in Sarnat et al. (2001) contains extensive results on the wintertime linear

13   relationships of personal total $PM_{2.5}$ exposure, exposure to estimated $PM_{2.5}$ of ambient origin,

14   personal $SO_4^=$ exposure, and personal elemental carbon (EC) exposure, versus ambient

15   concentrations of the gaseous co-pollutants. Many of these are statistically significant: negative

16   relationships of exposure to all of these particle components vs. ambient O_3, positive

17   relationships of personal exposure to EC and to estimated $PM_{2.5}$ of ambient origin versus NO_2 or

18   CO, and negative relationships of exposure to $SO_4^=$ and estimated $PM_{2.5}$ of ambient origin versus

19   ambient SO_2. However, as noted above, and as done by the authors in Figure 2, comparison of

20   personal exposures of the gaseous co-pollutants to these particle components might be more

21   useful in evaluating the question proposed by the authors: are gases confounders or surrogates of

22   fine particles or fine particle components?

23

24   *8.4.2.5.3 Confounding of co-pollutant effects arising from the spatial distribution of particles*
25   *and gases.*

26   We focus here mainly on the question of co-pollutant exposures as a potential confounder

27   of PM exposure, identified in the previous sections. There is a component of total exposure to

28   NO_2, CO, and other pollutants derived from ambient air most easily detected in the vicinity of

29   strong sources, such as the large number of automobiles and heavy-duty vehicles on major

30   highways or trunk roads near the exposed populations. The link to human health effects, if any,

31   would require satisfying three steps: (a) co-pollutant concentrations are high near certain line or

32   point sources, and decrease with increasing distance from the source much more rapidly than

1 does the PM_{10} or $PM_{2.5}$ concentration decrease with increasing distance; (b) humans residing near

2 strong sources are more highly exposed to co-pollutants than those living farther away; and

3 (c) increased risks of adverse health effects attributable to the co-pollutants occur in proximity to

4 stronger sources of the co-pollutants. For this reason, one may attribute some the difficulties in

5 interpreting the findings of multi-pollutant PM epidemiology models including co-pollutants as

6 spatial "measurement errors" associated with the non-uniform distribution of the co-pollutants in

7 an urban area. Thus, there may be a reduced likelihood that central site co-pollutant monitors

8 will accurately characterize population exposure compared to the ability of central site PM

9 monitors to characterize PM population exposure.

10 Recent reviews about traffic-oriented concentration gradients and exposures to other

11 pollutants have been published by van Wijnen and van der Zee (1998) and by Monn (2001).

12 Location effects are particularly noticeable at the neighborhood level if there is a strong line

13 source (arterial street or freeway, for example) or point source (fossil-fuel-burning power plant,

14 for example) near the micro-environment. Some studies provide quantitative relationships

15 between distance from a heavily traveled roadway and concentrations of various pollutants (van

16 Wijnen and van der Zee, 1998).

17 The spatial correlations for $PM_{2.5}$ were generally higher than for those of PM_{10} in the

18 PTEAM Riverside study (Clayton et al., 1993; Wallace, 1996) and in Philadelphia (Burton et al.,

19 1996; Wilson and Suh, 1997). However, larger spatial variations may occur for particles with

20 important local sources, such as highways carrying a large number of diesel trucks. Where PM_{10}

21 is dominated by coarse particles, substantial variations (±20%) occurred between pairs of

22 monitors within 4 to 14 km in California's San Joaquin Valley (Blanchard et al., 1999). Several

23 European studies have found modest variations in ambient PM_{10} concentrations for residences

24 and housing close to roadways (Kingham et al., 2000, for Huddersfield, U.K.; Monn et al., 1997,

25 for Zurich), but large differences in NO_2 concentrations occurred within a few meters of a Swiss

26 street during summer (Monn et al., 1997). The Monn results are shown as Figure 8-27. The

27 location and behavior of participants in a personal exposure study, as well as the spatial aspects

28 of socioeconomic differences in exposure (Rotko et al., 2000), may be important in defining

29 differences in exposure among sub-populations in an epidemiology study.

30 Numerous studies on personal exposure to airborne particles are discussed in detail in

31 Chapter 5. There is little doubt that elevated ambient concentrations of sulfates and fine particles
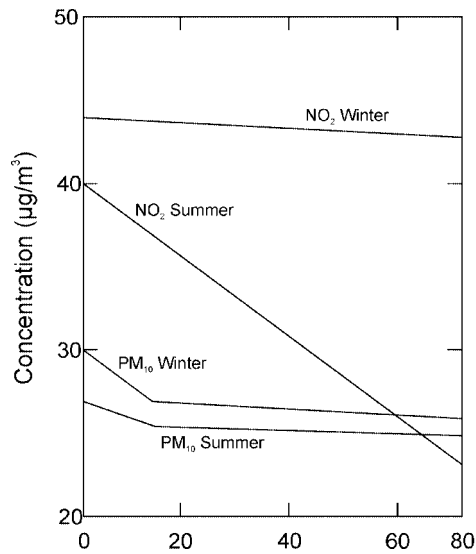
Figure 8-27. Concentration of PM$_{10}$ and NO$_2$ versus distance.

Source: Monn et al. (2000).

1   are closely related to elevated personal exposures to fine particles of ambient origin and to

2   elevated personal exposure to sulfates. In general, concentrations of ambient fine particles and

3   sulfates are more closely correlated to distance from a major highway or other sources than are

4   PM$_{10\text{-}2.5}$, NO$_2$, and CO, whose concentrations decrease with increasing distance. Rotko et al. also

5   reported that PM$_{2.5}$ was more uniformly distributed in Helsinki than was NO$_2$.

6   Janssen et al. (2001) evaluated personal indoor and outdoor NO$_2$ and PM$_{2.5}$ concentrations

7   at 24 schools located within 400 m of 22 different stretches of freeway in the Netherlands.

8   Indoor PM$_{2.5}$ exposure was correlated with the distance from the school to the freeway and was

9   moderately correlated with the truck traffic volume, but not with the total or car traffic volume.

10   Indoor NO$_2$ concentration was significantly associated with car traffic volume and with percent

11   of time downwind, but not with distance from the freeway or with truck traffic volume. Outdoor

12   NO$_2$ concentration was significantly correlated only with percent of time downwind from the

13   freeway. PM$_{2.5}$ concentrations indoors and outdoors were both significantly correlated with truck

14   traffic and distance from the freeway, but not with car traffic (at $P < 0.05$) or downwind

15   percentage.

1   Traffic-oriented health effects were reviewed by Wjst. et al. (1993) and by van Wijnen and

2   van der Zee (1998). New studies have appeared since then, including those by Venn et al. (2001)

3   and Roemer and van Wijnen (2001). The study by Roemer and van Wijnen is notable for three

4   reasons: (i) the endpoint is total mortality, as a more serious outcome than respiratory symptoms

5   in children; (ii) the populations in the study were divided into a "traffic" population living along

6   roads with traffic volume greater than 10,000 vehicles per day (about 10 percent of the total

7   population of Amsterdam) and a background population; (iii) measured air pollution

8   concentrations of BS, PM_{10}, NO_2, NO, CO, SO_2, and O_3 (8-hour mean) were available for the

9   background populations, and BS, NO_2, NO, CO, SO_2, and O_3 for the "traffic" populations. All of

10   the pollutant concentrations except for O_3 were higher for the "traffic" sites than for the

11   background sites. The excess risk rates in Table 3 in Roemer and van Wijnen (2001) for Black

12   Smoke (lags 1 and 2) were much higher and, for NO_2 (lag 1) somewhat higher, than in the traffic

13   population. However, the statistically significant risk rates for the total population using the

14   "traffic" air pollution sites was lower than those using the background sites. No results were

15   reported for risk rates for the "traffic" population using traffic monitor sites, but the background

16   monitor concentrations were moderately correlated with those at the traffic monitoring sites.

17

18   **8.4.2.6 Assessment of Confounding by Factor Analysis**

19   How can one assess confounding in a single-city study if PM and its gaseous co-pollutants

20   are inextricably mixed in the urban atmosphere? One possibility is to make use of the correlation

21   structure of the data by extracting its principal components, or factors if the principal components

22   are rotated to provide a clearer picture of the main components. The principal components (p.c.)

23   or factors are linear combinations of the pollutant concentrations and are exactly independent for

24   p.c. and nearly so for rotated factors. An important advantage of this method is that there is no

25   problem of instability when all or most p.c. or factors are used in a multi-p.c. model. Several

26   variations of this approach have been used in PM epidemiology studies. Ozkaynak et al. (1996)

27   studied the relationship between mortality, air pollution, and weather using factor analysis

28   methods, where the factors were constructed from a particle index CoH, CO, and weather

29   variables. The analyses in Laden et al. (2000) and Tsai et al. (1999, 2000) used factors based on

30   chemical elements in fine particles for each day for which there was a fine particle filter sample.

31   Laden et al. (2000) identified up to seven sources in six cities, with some differences in the target

1   elements for sources across the cities. Three sources were present in all cities (mobile sources,

2   coal combustion, crustal particles). Poisson regression models were fitted to mortality data with

3   all source factors included simultaneously. Positive and statistically significant effects were

4   found for the motor vehicle and coal combustion sources in most cities, but not the crustal

5   source. These studies did not include gaseous pollutants.

6   Mar et al. (2000) developed a factor-analytic model for Phoenix, AZ, based on

7   12 components of particles and three gaseous pollutants (CO, NO2, SO2) measured on the same

8   day. They reported relative risks of total and cardiovascular mortality for five factors,

9   representing: motor vehicle exhaust and resuspended road dust; soil; vegetative burning; local

10 sources of SO_2; and regional sulfate. The results reported in Tables 9 of Mar et al. (2000) are for

11 single-factor models. The authors state that regression analysis with all of the factors included in

12 a multisource model produced similar results.

13   This is a promising approach to analyzing multi-pollutant models and, in principle, could

14 be used in other studies with particles and gaseous criteria pollutants, even if little or no chemical

15 composition data were available. At the very least, evaluating the principal components of a

16 particle-gas mixture might help to identify which combinations of particles and gases are most

17 difficult to separate statistically in a regression analysis.

18

19 **8.4.2.7 Simulation Analysis of Confounding**

20   Since no single model specification can a priori be designated as "correct" in addressing

21 confounding effects of co-pollutants, discrepancies in results among studies, even for the same

22 dataset, are to be expected. While any assessment of relative "adequacy" of these alternative

23 model specifications is difficult with observational data, the implication of "inadequate" model

24 specifications may be studied through simulations using synthetic data in which the "correct"

25 model is known. Chen et al. (1999) conducted such simulations using a synthetic data set in

26 which the causal variables are known, and the effects of model misspecification were studied in

27 the presence of two variables (x_1 and x_2), with varying levels of correlation, in a Poisson model.

28 They considered three situations: (1) *model underfit*, in which mortality was generated with both

29 x_1 and x_2, but regressed only on x_1; (2) *model overfit*, in which mortality was generated with only

30 x_1, but regressed on both x_1 and x_2; and (3) *model misfit*, in which mortality was generated with

31 either x_1 or x_2 but regressed on the other variable. They observed that the confounding of

1   covariates in an overfitted model does not bias the estimated coefficients but does reduce their

2   significance; and that the effect of model underfit or misfit leads not only to erroneous estimated

3   coefficients but also to erroneous significance. Based on these observations, Chen et al.

4   suggested that "models which use only one or two air quality variables (such as PM_{10} and SO_2)

5   are probably unreliable, and that models containing several correlated and toxic or potentially

6   toxic air quality variables should also be investigated...". While conceptually useful, this

7   simulation study ignored one factor that is crucial in evaluating the implication of confounding,

8   the relative error. For example, including several correlated pollutants in a regression model may

9   lead to erroneous inferences, unless one considers the relative error associated with each of the

10   pollutants.

11

12   **8.4.2.8 Discussion**

13   In the preceding several section, a number of methods for evaluating the potential for

14   gaseous co-pollutants to confound particle effects were discussed. Multi-pollutant models may

15   be sensitive to multi-colinearity (high correlations among particle and gaseous pollutant

16   concentrations), and to so-called "measurement errors", possibly associated with spatial

17   variability. Combining multi-pollutant models across several cities may not improve the

18   precision of the mean PM effect size estimate combined, if the differences among the cities is as

19   large or larger in the multi-pollutant models as in the single-pollutant PM model. Second-stage

20   regressions have been useful in identifying effect modifiers in the NMMAPS and APHEA 2

21   studies, but may not, in general, provide a solution to the problem that confounding of effects is a

22   within-city phenomenon. Furthermore, the correlations among pollutants may change from

23   season to season and from place to place, suggesting that confounding as indicated by co-

24   linearity is not always the same.

25   Two promising approaches are also discussed, the first based on personal exposures to

26   particles and gases of three panels of participants in Baltimore, MD (Sarnat et al., 2000, 2001).

27   This directly addresses the premise that if individuals are not exposed to a potential confounder,

28   then it cannot really be a confounder of the presumed causal effect. While the results in this

29   paper support the conclusion that personal exposure to sulfates, fine particles, and PM_{10} are well

30   correlated with the corresponding fixed site ambient concentrations, the correlations are much

31   lower for $PM_{10-2.5}$, O_3, and NO_2. There is however a great deal of variation from one of three

1   two-week panels from one season to the next. The sample size is small (N = 56), but did detect

2   marginally significant associations between personal and ambient NO_2 for the personal-ambient

3   correlation, although much lower than for particles. There were, however, a number of

4   residences in which personal and ambient NO_2 were highly correlated. This has been known to

5   happen in other studies when the residences are close to a major road, which describes several

6   members in the three cohorts (health elderly adults, adults with COPD, children 9-13 years.)

7   The other promising approach is to use principal component or factor analysis to determine

8   which combinations of gaseous criteria pollutants and PM size fractions or chemical constituents

9   together cannot be easily disentangled, and which pollutants are substantially independent of the

10   linear combinations of the others. For example, Mar et al. (2000) shows independent effects of

11   regional sulfate, motor vehicle-related particles, particles from vegetive burning, and PM_{10-25} for

12   cardiovascular mortality in Phoenix.

13

8.4.3 Role of Particulate Matter Components

15   In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive

16   associations between ambient PM_{10} concentrations and various health indicators, e.g., mortality,

17   hospital admissions, respiratory symptoms, pulmonary function decrements, etc.. A somewhat

18   more limited number of studies were then available which substantiated mortality and morbidity

19   associations with various fine particle indicators (e.g., $PM_{2.5}$, sulfate, H^+, etc.); and only one, the

20   Harvard Six Cities analysis by Schwartz et al. (1996a), evaluated relative contributions of the

21   fine ($PM_{2.5}$) versus the coarse ($PM_{10-2.5}$) fraction of PM_{10}, with $PM_{2.5}$ appearing to be associated

22   more strongly with mortality effects than $PM_{10-2.5}$. Lastly, only a very few studies seemed to be

23   indicative of possible coarse particle effects, e.g., increased asthma risks associated with quite

24   high PM_{10} concentrations in a few locations where coarse particles strongly dominated the

25   ambient PM_{10} mix.

26

8.4.3.1 Fine- and Coarse-Particle Effects on Mortality

28   A greatly enlarged and still rapidly growing number of new studies published since the

29   1996 PM AQCD provide much new evidence further substantiating ambient PM associations

30   with increased human mortality and morbidity. As indicated in Table 8-1, most newly reported

31   analyses, with few exceptions, continue to show statistically significant associations between

1   short-term (24-h) PM concentrations and increases in daily mortality in many U.S. and Canadian

2   cities (as well as elsewhere). Also, the reanalyses of Harvard Six City and ACS study data

3   substantiate the original investigator's findings of long-term PM exposure associations with

4   increased mortality as well.

5

6   *8.4.3.1.1 Effects on Total Mortality*

7   The effects estimates from the newly reported studies are generally consistent with those

8   derived from the earlier 1996 PM AQCD assessment, which reported risk estimates for excess

9   total (nonaccidental) deaths associated with short-term PM exposures as generally falling within

10   the range of ca. 1.5 to 8.5% per 50 μg/m^3 PM$_{10}$ (24-h) increment and ca. 2.5 to 5.5% increase per

11   25 μg/m^3 PM$_{2.5}$ (24-h) increment.

12   Several new PM epidemiology studies which conducted time-series analyses in multiple

13   cities were noted to be of particular interest, in that they provide evidence of effects across

14   various geographic locations (using standardized methodologies) and more precise pooled effect

15   size estimates with narrow confidence bounds, reflecting the typically much stronger power of

16   such multi-city studies over individual-city analyses to estimate a mean effect. Based on pooled

17   analyses across multiple cities, the percent total (non-accidental) excess deaths per 50 μg/m^3

18   PM$_{10}$ increment were estimated in different multi-city analyses to be: (a) 2.3% in the 90 largest

19   U.S. cities; (b) 3.4% in 10 large U.S. cities; (c) 3.5% in the 8 largest Canadian cities; and

20   (d) 2.0% in European cities.

21   Many new individual-city studies found positive associations (most statistically significant

22   at $p < 0.05$) for the PM$_{2.5}$ fraction, with effect size estimates typically ranging from ca. 2.0 to ca.

23   8.5% per 25 μg/m^3 PM$_{2.5}$ for U.S. and Canadian cities. Of the 10 or so new analyses that not

24   only evaluated PM$_{10}$ effects but also made an effort to compare fine versus coarse fraction

25   contributions to total mortality, only two are multi-city analyses yielding pooled effects

26   estimates: (a) the Klemm and Mason (2000) recomputation of Harvard Six Cities data,

27   confirming the original published findings by Schwartz et al. (1996a); and (b) the Burnett et al.

28   (2000) study of the 8 largest Canadian cities. Both of these studies found roughly comparable,

29   statistically significant excess risk estimates for PM$_{2.5}$, i.e., approximately 3% increased total

30   mortality risk per 25 μg/m^3 PM$_{2.5}$ increment.

1   With regard to possible coarse particle short-term exposure effects on mortality, in those

2   new studies which evaluated $PM_{10-2.5}$ effects as well as $PM_{2.5}$ effects, the coarse particle ($PM_{10-2.5}$)

3   fraction was also consistently positively associated with increased total mortality, albeit the

4   coarse fraction effect size estimates were generally less precise than those for $PM_{2.5}$ and

5   statistically significant at $p < 0.05$ in only a few studies (Figure 8-6). Still, the overall picture

6   tends to suggest that excess total mortality risks may well reflect actual coarse fraction particle

7   effects, in at least some locations. This may be most consistently the case in arid areas, e.g., in

8   Mexico City, Santiago, Chile, or in the Phoenix area (as shown in Mar et al., 2000). On the other

9   hand, significant (or nearly significant) elevations in coarse PM-related total mortality risks have

10   also been detected for Steubenville, PH (an eastern U.S. urban area in the Harvard Six City

11   Study), as shown by Schwartz et al. (1996a). These results may reflect contamination of later-

12   resuspended coarse PM by metals in fine PM emitted from smelters (Phoenix) or steel mills

13   (Steubenville) that was earlier deposited on nearby soils. Excess total mortality risks associated

14   with short-term (24-h) exposures to coarse fraction particles capable of depositing in the lower

15   respiratory tract generally fall in the range of 0.5 to 6.0% per 25 $\mu g/m^3$ PM_{10-25} increment for U.S.

16   and Canadian cities.

17   Three new papers provide particularly interesting new information on relationships between

18   short-term coarse particle exposures and total elderly mortality (age 65 and older), using

19   exposure TEOM data from the EPA ORD NERL monitoring site in Phoenix, AZ. Each used

20   quite different models but each reported statistically significant relationships between mortality

21   and coarse PM, specifically $PM_{10-2.5}$, an indicator for the thoracic fraction of coarse-mode PM.

22   Smith et al. (2000), using a three-day running average as the exposure metric, performed

23   linear regression of the square root of daily mortality on the long-term trend, meteorological and

24   PM-based variables. Two mortality variables were used, total (non-accidental) deaths for the city

25   of Phoenix and the same for a larger, regional area. Using a linear analysis, effects based on

26   coarse PM were statistically significant for both regions, whereas effects based on fine PM

27   ($PM_{2.5}$) were not. However, when the possibility of a nonlinear response was taken into account,

28   no evidence was found for a nonlinear effect for coarse PM, but fine PM was found to have a

29   statistically significant effect for concentration thresholds of 20 and 25 $\mu g/m^3$. There was no

30   evidence of confounding between fine and coarse PM, suggesting that fine and coarse PM are

31   "essentially separate pollutants having distinct effects". Smith et al. (2000) also observed a

1   seasonal effect for coarse PM, the effect being statistically significant only during spring and

2   summer. Based on a principal component analysis of elemental concentrations, crustal elements

3   are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000) felt

4   that the implication that crustal, rather than anthropogenic elements, were responsible for the PM

5   mortality was counterintuitive.

6   Clyde et al. (2000) used a more conventional model, a Poisson regression of log deaths on

7   linear PM variables; but they employed Bayesian model averaging to consider a wide variety of

8   variations in the basic model. They considered three regions: the Phoenix metropolitan area;

9   a small subset of zip code to give a region presumably with uniform $PM_{2.5}$; and a still smaller zip

10   code region surrounding the monitoring site (thought to be uniform as to PM_{10} concentrations).

11   The models considered lags of 0, 1, 2, or 3 days but only for single day PM variables (no running

12   averages as used by Smith et al., 2000). A PM effect with a reasonable probability was found

13   only in the uniform $PM_{2.5}$ region and only for coarse PM.

14   Mar et al. (2000) used conventional Poisson regression methods and limited their analyses

15   to the smallest area (called Uniform PM_{10} by Clyde et al.). They reported modeling data for lag

16   days 0 to 4. Coarse fraction PM was marginally significant on lag day 0. No direct fine particle

17   measures were statistically significant on day 0. A regional sulfate factor determined from

18   source apportionment, however, was statistically significant. No correlations were reported for

19   the source apportionment factors, but the correlation coefficient between sulfur (S) in $PM_{2.5}$ (as

20   measured by XRF) with coarse fraction PM was only 0.13, suggesting separate and distinct

21   effects for regional sulfate and coarse fraction PM.

22   The above three studies of PM- total mortality relationships in Phoenix tend to suggest a

23   statistical association of coarse fraction PM with total elderly mortality in addition to and

24   different from any relationship with fine PM, fine PM components, or source factors for fine PM.

25   With regard to long-term PM exposure effects on total (non-accidental) mortality, the

26   newly available evidence from the HEI Reanalyses of Harvard Six Cities and ACS data (and

27   extensions, thereof), substantiate well associations attributable to chronic exposures to inhalable

28   thoracic particles (indexed by PM_{15} or PM_{10}) and the fine fraction of such particles (indexed by

29    $PM_{2.5}$ and/or sulfates). Statistically significant excess risk for total mortality was shown by the

30   reanalyses to fall in the range of 4-18% per 20 μg/m^3 $PM_{15/10}$ increment and 14-28% per

31   20 μg/m^3 $PM_{2.5}$ increase, thus suggesting likely stronger associations with fine versus coarse

1   fraction particles. Significant fine PM associations with total mortality were also found in the

2   latest reported AHSMOG results for males, but not in females.

3   Other recent studies on the relation of mortality to particle composition and source (Laden

4   et al., 2000; Mar et al., 2000; Özkaynak et al., 1996; Tsai et al., 2000) suggest that particles from

5   certain sources may have much higher potential for adverse health effects than others, as

6   delineated by source-oriented evaluations involving factor analyses. Laden et al. (2000)

7   conducted factor analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study

8   data for 1979-1988. In the analysis for all six cities combined, the excess risk for daily mortality

9   was estimated to be 3.4% (CI, 1.7 to 5.2) per 10 $\mu g/m^3$ increment in a mobile source factor; 1.1%

10   (CI, 0.3 to 2.0) per 10 $\mu g/m^3$ for a coal source factor, and -2.3% (CI, -5.8 to 1.2) per 10 $\mu g/m^3$

11   for a crustal factor. There was large variation among the cities and some suggestion of an

12   association with a fuel oil factor identified by V or Mn, but it was not statistically significant.

13   Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995-1997 fine

14   particle elemental components and gaseous pollutants (CO, NO_2, SO_2) in an area of Phoenix, AZ,

15   close to the air pollution monitors. The $PM_{2.5}$ constituents included sulfur, Zn, Pb, soil-corrected

16   potassium, organic and elemental carbon, and a soil component estimated from oxides of Al, Si,

17   Ca, Fe, and It. Based on models fitted using one pollutant at a time, statistically significant

18   associations were found between total mortality and PM_{10}, CO (lags 0 and 1), NO_2 (lags 0, 1, 3,

19   4), S (negative), and soil (negative). Statistically significant associations were also found

20   between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4),

21   $PM_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $PM_{10-2.5}$ (lag 0), and elemental, organic, or total carbon.

22   Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings

23   on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust

24   factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2), and a regional sulfate

25   factor (with a high loading on S). However, total mortality was negatively associated with a soil

26   factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated

27   with the regional sulfate factor.

28   Tsai et al. (2000) analyzed daily time series of total and cardiorespiratory deaths, using

29   short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to

30   inhalable particle mass (PM_{15}) and fine particle mass ($PM_{2.5}$), the study evaluated data for metals

31   (Pb, Mn, Fe, Cd, V, Ni, Zn, Cu) and for three fractions of extractable organic matter. Factor

1   analyses were carried out using the metals, CO, and sulfates. The most significant sources or

2   factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd

3   processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO, industrial

4   Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and sulfates

5   were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden oil

6   burning and motor vehicle emissions predicted total mortality, but copper showed a marginal

7   negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of

8   cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn

9   showed marginal negative associations with mortality, as did industrial sources traced by Cu.

10   The set of results from the above factor analyses studies do not yet allow one to identify

11 with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless,

12 some commonalities across the studies seem to highlight the likely importance of mobile source

13 and other fuel combustion emissions (and apparent lesser importance of crustal particles) as

14 contributing to increased total or cardiorespiratory mortality.

15

16 *8.4.3.1.2 Effects on Cause-Specific Mortality*

17 **Cardiovascular- and Respiratory-Related Mortality**

18   Numerous new studies have evaluated PM-related effects on cause-specific mortality.

19 Most all report positive, often statistically significant (at $p < 0.05$), short-term (24-h) PM

20 exposure associations with cardiovascular (CVD)- and respiratory-related deaths. Cause-specific

21 effects estimates appear to mainly fall in the range of 3.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for

22 cardiovascular or combined cardiorespiratory mortality and 2.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$

23 for respiratory mortality in U.S. cities. Effect size estimates for the coarse fraction ($PM_{10-2.5}$) for

24 cause-specific mortality generally fall in the range of ca. 3.0 to 8.0% for cardiovascular and ca.

25 3.0 to 16.0% for respiratory causes per 25 $\mu g/m^3$ increase in $PM_{10-2.5}$.

26   Also of particular interest, the above noted study by Mar et al. examined the associations of

27 a variety of PM indicators with cardiovascular mortality (for age ≥ 65), again in the zip code area

28 near the Phoenix monitoring site. For this end point, coarse PM was statistically significant on

29 lag day 0 but not on subsequent lag days. $PM_{2.5}$ and a number of fine PM indicators were

30 statistically significant on lag day 1 but not on lag day 0. This suggests a distinct and separate

31 relationship of $PM_{2.5}$ and $PM_{10-2.5}$. As in the case of total mortality, the only fine PM indicator

1   found to be statistically significant on lag day 0 was regional sulfate. However, the low

2   correlation coefficient between S in $PM_{2.5}$ and $PM_{10-2.5}$ (r = 0.13) suggests that the two

3   relationships represent different sets of deaths. Thus, there is some evidence suggesting that the

4   risk of cardiovascular mortality , as well as that of total mortality, may be statistically associated

5   with $PM_{10-2.5}$ and that this relationship may be independent of any relationships with fine particle

6   indicators.

7

8   *Long-Term PM Exposure and Lung Cancer*

9   Of particular interest with regard to PM-related effects on cause-specific mortality is a

10   growing body of evidence linking long-term PM exposure with increased risk of lung cancer.

11   Historical evidence has included studies of lung cancer trends, studies of occupational groups,

12   comparisons of urban and rural populations, and case-control and cohort studies using diverse

13   exposure metrics (Cohen and Pope, 1995). Table 8-39 (derived from Cohen, 2000) indicates

14   that, despite possible problems with respect to potential errors in exposure and other risk factor

15   measurement errors, numerous past ecological and case-control studies of PM and lung cancer

16   have generally indicated a lung cancer RR greater than 1.0 to be associated with living in areas

17   indicated as having higher PM exposures.

18   Prospective cohort studies offer a potentially more powerful approach to evaluate the

19   apparent association between PM exposures and the development of lung cancer. The 1996 PM

20   AQCD (U.S. Environmental Protection Agency, 1996a) summarized three of these more

21   elaborate studies that carefully evaluated the effects of PM air pollution exposure on lung cancer

22   using the prospective cohort design. In the Adventist Health Smog Study (AHSMOG), Abbey

23   et al. (1991) followed a cohort of Seventh Day Adventists, whose extremely low prevalence of

24   smoking and uniform, relatively healthy dietary patterns reduce the potential for confounding by

25   these factors. Excess lung cancer incidence was observed in females in relation to both particle

26   (TSP) and ozone exposure after 6 years follow up time. Dockery et al. (1993) reported the

27   results of a 14- to 16-year prospective follow-up of 8,111 adults living in six U.S. cities that

28   evaluated associations between air pollution and mortality. After controlling for individual

29   differences in age, sex, cigarette smoking, BMI, education, and occupational exposure, Dockery

30   et al. (1993) found an elevated but non-significant risk for lung cancer (RR = 1.37; 95%CI = 0.81

31   to 2.31) for a difference in $PM_{2.5}$ pollution equal to that of the most polluted versus the least

**TABLE 8-39. SUMMARY OF PAST ECOLOGIC AND CASE-CONTROL
EPIDEMIOLOGIC STUDIES OF OUTDOOR AIR AND LUNG CANCER**

Study Type	Authors	Locale	Exposure Classification	Rate Ratio (95% CI)
Ecologic	Henderson et al., 1975	Los Angeles, CA	High PAH Areas	1.3 @ 96-116 ug/m^3 TSP (CI: N/A)
	Buffler et al., 1988	Houston, TX	TSP by Census Tract	1.9 @ 16 ug/m^3 TSP (CI: N/A)
	Archer, 1990	Utah	TSP by county	1.6@ 85 ug/m^3 TSP (CI: N/A)
Case-Control	Pike et al., 1979	Los Angeles	BAP Geo. Areas	1.3 @ 96-116 ug/m^3 TSP
	Vena, 1982	Buffalo, NY	TSP Geo. Areas	1.7 @ 80-200 ug/m^3 TSP (CI: 1.0-2.9)
	Jedrychowski, et al., 1990	Cracow, Poland	TSP and SO_2 Geo. Areas	1.1@ TSP>150 ug/m^3 (CI: N/A)
	Katsouyanni, et al., 1990	Athens, Greece	Soot Concentration Geo. Areas	1.1@ soot up to 400 ug/m^3 (CI: N/A)
	Barbone et al., 1995	Trieste, Italy	High Particle Deposition Areas	1.4 @ >0.3 g/m^2/day (CI: 1.1-1.8)
	Nyberg et al., 2000	Stockholm, Sweden	High NO_2 Areas	1.3 (CI: 0.9-1.9)

Source: Cohen (2000).

1 polluted city. Pope et al. (1995) similarly analyzed $PM_{2.5}$ and sulfate ($SO_4^=$) air pollution as

2 predictors of mortality in a prospective study of 7-year survival data (1982 to 1989) for about

3 550,000 adult volunteers obtained by the American Cancer Society (ACS). Both the ACS and

4 Harvard studies have been subjected to much scrutiny, including an extensive independent audit

5 and re-analysis of the original data (Krewski et al., 2000) that confirmed the originally published

6 results. The ACS study controlled for individual differences in age, sex, race, cigarette smoking,

7 pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education,

8 BMI, and alcohol use. Lung cancer mortality was significantly associated with particulate air

9 pollution when $SO_4^=$ was used as the index,, but not when $PM_{2.5}$ mass was used as the index for a

10 smaller subset of the study population that resided in metropolitan areas where $PM_{2.5}$ data were

11 available from the Inhalable Particle (IP) Network. Thus, while these prospective cohort studies

1   have also indicated that long-term PM exposure is associated with an increased cancer risk, the

2   effect estimates were generally not statistically significant, quite possibly due to inadequate

3   statistical power by these studies at that time (e.g., due to inadequate population size and/or

4   follow-up time for long-latency cancers).

5   The AHSMOG investigators have re-examined the association between long-term PM

6   exposure and increased risk of both lung cancer incidence and lung cancer mortality in

7   nonsmokers using longer-term follow-up of this cohort and improved analytical approaches.

8   Beeson et al. (1998) considered this cohort of some 6,338 nonsmoking, non-Hispanic, white

9   Californian adults, ages 27-95, that was followed from 1977 to 1992 for newly diagnosed

10   cancers. Incident lung cancer in males was positively and significantly associated with IQR

11   increases for mean concentrations of PM_{10} (RR = 5.21; 95% CI =1.94-13.99). For females in the

12   cohort, incident lung cancer was positively associated with Inter-Quartile Range (IQR) increases

13   for SO_2 (RR = 2.14; CI, 1.36-3.37) and IQR increases for PM_{10} exceedance frequencies of 50

14   ug/m^3 (RR = 1.21; 95% CI = 0.55-2.66) and 60 ug/m^3 (RR = 1.25; 95% CI = 0.57-2.71). Thus,

15   increased risks of incident lung cancer were deemed by the authors to be associated with elevated

16   long-term ambient concentrations of PM_{10} and SO_2 in both genders. The higher PM_{10} risk effect

17   estimate for cancer in males appeared to be partially due to gender differences in long-term air

18   pollution exposures.   Abbey et al. (1999) also related long-term ambient concentrations of PM_{10},

19   $SO_4^=$, SO_2, O_3, and NO_2 to 1977-1992 mortality in the AHSMOG cohort. After adjusting for a

20   wide range of potentially confounding factors, including occupational and indoor sources of air

21   pollutants, PM_{10} showed a strong association with lung cancer deaths in males (PM_{10} IQR

22   RR=2.38; 95% CI: 1.42 - 3.97). In this cohort, males spent more time outdoors than females,

23   thus having higher estimated air pollution exposures than the cohort females. Ozone showed an

24   even stronger association with lung cancer mortality for males, and SO_2 showed strong

25   associations with lung cancer mortality for both sexes. The authors reported that other pollutants

26   showed weak or no association with mortality. Therefore, increases in both lung cancer

27   incidence and lung cancer mortality in the extended follow-up analysis of the AHSMOG study

28   were found to be most consistently associated with elevated long-term ambient concentrations of

29   PM_{10} and SO_2, especially among males.

30   A recent follow-up analysis of the major ACS study by Pope et al. (2002) responds to a

31   number of criticisms previously noted for the earlier ACS analysis (Pope et al., 1995) in the 1996

1   PM AQCD (U.S. Environmental Protection Agency, 1996a), most notably by including

2   examinations of other pollutants, better occupational indices, and diet information, while also

3   addressing possible spatial auto-correlations due to regional location. The recent extension of the

4   ACS study includes approximately 500,000 adult men and women drawn from ACS-CPS-II

5   enrollment and follow-up during 1982-1998. This new analysis of the ACS cohort substantially

6   expands the prior analysis, including: (1) a more than doubling of the follow-up time to 16 years

7   (and a more than tripling of the number of deaths in the analysis); (2) substantially expanded

8   exposure data, including gaseous co-pollutant data and new $PM_{2.5}$ data collected in 1999-2001;

9   (3) improved control of occupational exposures; (4) incorporation of dietary variables that

10   account for total fat consumption, as well as consumption of vegetables, citrus and high-fiber

11   grains; and (5) utilization of recent advances in statistical modeling, including the incorporation

12   of random effects and non-parametric spatial smoothing components in the Cox proportional

13   hazards model.

14   In this extended ACS analysis, it was found that long-term exposure to air pollution, and

15   especially to $PM_{2.5}$, is associated with increased annual risk of mortality. With the longer 15-year

16   follow-up period and with improved metrics of $PM_{2.5}$ exposures, this study for the first time

17   detected a statistically significant association between living in a city with higher $PM_{2.5}$ and

18   increased risk of dying of lung cancer. Each 10 ug/m^3 elevation in annual average fine PM was

19   associated with a 13 percent (95% CI=4%-23%) increase in lung cancer mortality. Coarse

20   particles and gaseous pollutants were generally not significantly associated with excess lung

21   cancer mortality. $SO_4^=$ was significantly associated with mortality and lung cancer deaths in this

22   extended data set, yielding RR's consistent with (i.e., not significantly different from) the $SO_4^=$

23   RR's reported in the previously published 7-year follow-up (Pope et al, 1995). However, while

24   $PM_{2.5}$ was specific to the causes most biologically plausible to be influenced by air pollution in

25   this analysis (i.e., cardio-pulmonary and cancer), $SO_4^=$ was significantly associated with every

26   mortality category in this new analysis, including that for "all-other causes", This suggests that

27   the $PM_{2.5}$ associations found are more biologically plausible than the less specific $SO_4^=$

28   associations found. The $PM_{2.5}$ cancer risk appears greatest for non-smokers and among those

29   with lower socio-economic status (as indicated by lower educational attainment).

30   Overall, these new cohort studies confirm and strengthen the published older ecological and

31   case-control evidence indicating that living in an area that has experienced higher PM exposures

1   can cause a significant increase in the RR of lung cancer incidence and associated mortality.

2   In particular, the new ACS cohort analysis more clearly indicates that living in a city with higher

3   PM$_{2.5}$ levels is associated with an elevated risk of lung cancer amounting to an increase of some

4   10 to 15% above the lung cancer risk in a cleaner city.

5   With regard to specific ambient fine particle constituents that may significantly contribute

6   to the observed ambient PM-related increases in lung cancer, PM components of diesel engine

7   exhaust represent one class of likely important contributors. Diesel emission PM typically

8   comprises a noticeable fraction of ambient fine particles in many urban areas, having been

9   estimated to comprise from approximately 5 to 35% of ambient PM$_{2.5}$ in some U.S. urban areas

10   (see Chapter 3). Also, as discussed in a separate Health Effects Assessment of Diesel Engine

11   Exhaust (U.S. Environmental Protection Agency, 2002), extensive epidemiologic and toxicologic

12   evidence links diesel emissions (including fine PM components) to increased risk of lung cancer.

13

14   **8.4.3.1.3 Shortening-of-Life Associated With Long-Term Ambient Particulate**
15   **   Matter Exposure**

16   The public health burden of mortality associated with exposure to ambient PM depends not

17   only on the increased risk of death, but also on the length of life shortening that is attributable to

18   those deaths. However, the 1996 PM AQCD concluded that confident quantitive determination

19   of years of life lost to ambient PM exposure was not yet possible; life shortening may range from

20   days to years (U.S. Environmental Protection Agency, 1996a). Now, some newly available

21   analyses provide further interesting insights with regard to potential life-shortening associated

22   with chronic PM exposures.

23

24   *8.4.3.1.3.1 Life-Shortening Estimates Based on Semi-Individual Cohort Study Results*

25   Brunekreef (1997) reviewed the available evidence of the mortality effects of long-term

26   exposure to PM air pollution and, using life table methods, derived an estimate of the reduction

27   in life expectancy implied by those effect estimates. Based on the results of Pope et al. (1995)

28   and Dockery et al. (1993), a relative risk of 1.1 per 10 μg/m^3 exposure over 15 years was

29   assumed for the effect of PM air pollution on men 25-75 years of age. A 1992 life table for men

30   in the Netherlands was developed for 10 successive five-year categories that make up the

31   25-75 year old age range. Life expectancy of a 25 year old was then calculated for this base case

32   and compared with the calculated life expectancy for the PM-exposed case, where the death rates

1   were increased in each age group by a factor of 1.1. A difference of 1.11 years was found

2   between the "exposed" and "clean air" cohorts' overall life expectancy at age 25. Looked at

3   another way, this implies that the expectation of the lifespan for persons who actually died from

4   air pollution was reduced by more than 10 years, since they represent a small percentage of the

5   entire cohort population. A similar calculation by the authors for the 1969-71 life table for U.S.

6   white males yielded an even larger reduction of 1.31 years for the entire population's life

7   expectancy at age 25. Thus, these calculations imply that relatively small differences in long-

8   term exposure to ambient PM can have substantial effects on life expectancy.

9

10 *8.4.3.1.3.2 Potential Effects of Infant Mortality on Life-Shortening Estimates*

11   Deaths among children can logically have the greatest influence on a population's overall

12 life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible

13 long-term air pollution exposure effects on the population aged <25 years. As discussed above,

14 some of the older cross-sectional studies and the more recent studies by Bobak and Leon (1992),

15 Woodruff et al. (1997), Bobak and Leon (1999), and Loomis et al. (1999) suggest that infants

16 may be among sub-populations notably affected by long-term PM exposure. Thus, although it is

17 difficult to quantify, any premature mortality that does occur among children due to long-term

18 PM exposure (as suggested by these new studies) would significantly increase the overall

19 population life shortening over and above that estimated by Brunekreef (1997) for long-term PM

20 exposure of adults aged 25 years and older.

21

22 **8.4.3.2 PM_{10}, $PM_{2.5}$ (Fine), and $PM_{10-2.5}$ (Coarse) Particulate Matter Effects on Morbidity**

23   At the time of the 1996 PM AQCD, fine particle morbidity studies were mostly limited to

24 Schwartz et al. (1994) , Neas et al. (1994, 1995); Koenig et al. (1993); Dockery et al. (1996); and

25 Raizenne et al. (1996); and discussion of coarse particles morbidity effects was also limited to

26 only a few studies (Gordian et al., 1996; Hefflin et al., 1994) which implicated $PM_{10-2.5}$ as a

27 possible important fraction of PM_{10}. Since the 1996 PM AQCD, several new studies have been

28 published in which newly available size-fractionated PM data allowed investigation of the effects

29 of both fine ($PM_{2.5}$) and coarse fraction ($PM_{10-2.5}$) particles. Fine (FP) and coarse fraction (CP)

30 particle results are noted below for studies by morbidity outcome areas, as follows:

1   cardiovascular disease (CVD) hospital admissions (HA's); respiratory medical visits and hospital

2   admissions; and respiratory symptoms and pulmonary function changes.

3   As discussed in Section 8.3.1 (on cardiovascular effects associated with acute ambient PM

4   exposure), an extensive new body of evidence has emerged since the 1996 PM AQCD that

5   evaluates PM_{10} effects on cardiovascular-related hospital admissions and visits. Especially

6   notable new evidence has been provided by several new multi-city studies (Schwartz, 1999;

7   Samet et al., 2000a,b) that yield pooled estimates of PM-CVD effects across numerous U.S.

8   cities and regions. These studies found not only significant PM associations, but also

9   associations with other gaseous pollutants as well, thus hinting at likely independent effects of

10   certain gases (O_3, CO, NO_2, SO_2) and/or interactive effects with PM. These and other individual-

11   city studies generally appear to confirm likely excess risk of CVD-related hospital admission for

12   U.S. cities in the range of 3-10% per 50 μg/m^3 PM_{10}, especially among the elderly ($\geq$ 65 yr).

13   In addition to the PM_{10} studies, several new U.S. and Canadian studies evaluated fine-mode

14   PM effects on cardiovascular outcomes. Moolgavkar (2000a) reported $PM_{2.5}$ to be significantly

15   associated with CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997a) reported that fine

16   particles were significantly associated with CVD HA in a single pollutant model, but not when

17   gases were included in multipollutant models for the 8 largest Canadian city data. Stieb et al.

18   (2000) reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED)

19   visits in single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported

20   that $PM_{2.5}$ measured by nepholonetry was associated with CVD HA for all ages and 65+ yr, but

21   not in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were

22   significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao

23   et al., 1999; Creason et al., 2001; Pope et al., 1999b,c) reported associations between increases in

24   $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (2000) reported a

25   negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate

26   variability measure). A recent study by Peters and colleagues (2001) reported significant

27   temporal associations between acute (2-h or 24-h) measures of $PM_{2.5}$ and myocardial infarction.

28   Overall, these new studies collectively appear to implicate fine particles, as well as possibly some

29   gaseous co-pollutants, in cardiovascular morbidity, but the relative contributions of fine particles

30   acting alone or in combination with gases such as O_3, CO, NO_2 or SO_2 remain to be more clearly

31   delineated and quantified. The most difficult issue relates to interpretation of reduced PM effect

1 size and /or statistical significance when co-pollutants derived from the same source(s) as PM are

2 included in multipollutant models.

3   Section 8.3.1 also discussed U.S. and Canadian studies that present analyses of coarse

4 fraction particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) found significant

5 positive associations of $PM_{10-2.5}$ with ischemic heart disease hospital admissions in Detroit

6 (RR = 1.10, CI 1.026, 1.18). Tolbert et al. (2000a) reported significant positive associations of

7 heart dysrhythmias with CP (p = 0.04) as well as for elemental carbon (p = 0.004), but these

8 preliminary results must be interpreted with caution until more complete analyses are carried out

9 and reported. Burnett et al. (1997b) noted that CP was the most robust of the particle metrics

10 examined to inclusion of gaseous covariates for cardiovascular hospitalization, but concluded

11 that particle mass and chemistry could not be identified as an independent risk factor for

12 exacerbation of cardiorespiratory disease in this study. Based on another Canadian study,

13 Burnett et al. (1999), reported statistically significant associations for CP in univariate models

14 but not in multipollutant models; but the use of estimated rather than measured PM exposures

15 indices limits the interpretation of the PM results reported.

16   The collective evidence reviewed above, in general, appears to suggest excess risks for

17 CVD-related hospital admissions of approximately 4.0 to 10% per 25 μg/m^3 $PM_{2.5}$ or $PM_{10-2.5}$

18 increment.

19   Section 8.3.2 also discussed new studies of effects of short-term PM exposure on the

20 incidence of respiratory hospital admissions and medical visits. Several new U.S. and Canadian

21 studies have yielded particularly interesting results suggestive of roles of both fine and coarse

22 particles in respiratory-related hospital admissions. In an analysis of Detroit data, Lippmann

23 et al. (2000) found comparable effect size estimates for $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess

24 risk for pneumonia hospital admissions (in no co-pollutant model) was 13% (CI 3.7, 22) per

25 25 μg/m^3 $PM_{2.5}$ and 12% (CI 0.8, 24) per 25 μg/m^3 $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not

26 highly correlated, the observed association between coarse particles and health outcomes were

27 possibly not confounded by smaller particles. Despite the greater measurement error associated

28 with $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10}, this indicator of the coarse particles within the

29 thoracic fraction was associated with some of the outcome measures. The interesting result is

30 that $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics, especially given the effect

31 estimates of $PM_{10-2.5}$ with pneumonia hospital admissions (lag 1; RR = 1.11, 95% CI: 1.006,

1   1.233). Burnett et al. (1997b) also reported PM (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) associations with

2   respiratory hospital admissions, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was

3   significant (RR = 1.13 for 25 $\mu g/m^3$; CI = 1.05 - 1.20); and inclusion of ozone still yielded a

4   significant coarse mass RR = 1.11 (CI = 1.04 - 1.19). Moolgavkar et al. (2000) showed the most

5   consistent association for PM_{10} across lags (0-4d), while $PM_{2.5}$ yielded the strongest positive PM

6   metric association at lag 3 days. Also, Moolgavkar (2000a) reported that, in Los Angeles, both

7   PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different lags for single

8   pollutant models but not in two pollutant models. Delfino et al. (1997) reported that both $PM_{2.5}$

9   and PM_{10} are positively associated with ED visits for respiratory disease. Morgan et al. (1998)

10   reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$ association with COPD hospital

11   admissions for 1-hr max PM that was more positive than 24-h average $PM_{2.5}$.

12   Some new studies appear to substantiate PM associations with asthma-related hospital

13   admissions. For example, Norris et al (1999) reported associations of emergency department

14   visits for asthma in children with both $PM_{2.5}$ and $PM_{10-2.5}$. Two other studies presented uniquely

15   different analyses of hospital admissions in the Seattle, Washington area. Sheppard et al. (1999)

16   studied relationships between PM metrics that included $PM_{10-2.5}$ and non-elderly adult hospital

17   admissions for asthma in the greater Seattle area and reported significant relative rates for PM_{10},

18   $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10-2.5}$, the relative risk was 1.04 (95% CI 1.01, 1.07).

19   In a different analysis, Lumley and Heagerty (1999) examined PM_1 and PM_{10-1} in the King

20   County, WA (Seattle) area during the same time period but for hospital admissions for overall

21   respiratory disease. Since only a significant hospital admission association was found with $PM_{1.0}$

22   and not PM_{10-1}, a dominant role by sub-micron particles in $PM_{2.5}$ - asthma HA association was

23   suggested, but this may not be an appropriate conclusion based on several differences between

24   the study analysis methods and differences between asthma versus respiratory outcome measures

25   used in the two Seattle studies. For a 16% decrease in PM_{10} levels, Friedman et al. (2001)

26   reported decreased hospital admissions for asthmatics during the Olympics in Atlanta.

27   Several other studies (Chen et al. 2000; Choudhury et al., 1997; Moolgavlar 2000a;

28   Lippsett et al., 1997) report results for areas (e.g., Reno-Sparks, NV; Anchorage, AK; Phoenix,

29   AZ; Santa Clara, CA) where coarse fraction particles tend to constitute a large fraction of PM_{10}

30   but no measures of $PM_{10-2.5}$ were available. These studies showing significant PM_{10} effects on

31   respiratory hospital admissions provide additional data suggestive of likely coarse fraction

1   particle effects on respiratory morbidity. It is possible that vegetative burning (e.g., wood) in

2   these western cities may produce coarse particles whose toxicity may differ from that of coarse

3   crustal fraction particles.

4   Thus, although PM_{10} mass has most often been implicated as the PM pollution index

5   affecting respiratory hospital admissions, the overall collection of new studies reviewed in

6   Section 8.3.2 appear to suggest relative roles for both fine and coarse PM mass fractions, such as

7   $PM_{2.5}$ and $PM_{10-2.5}$.

8   Section 8.3.3 assessed relationships between PM exposure on lung function and respiratory

9   symptoms. While most data examine PM_{10} effects, several studies also examined fine and coarse

10 fraction particle effects. Schwartz and Neas (2000) report that cough was the only response in

11 which coarse fraction particles appeared to provide an independent contribution to explaining the

12 increased incidence. The correlation between CM and $PM_{2.5}$ was moderate (0.41). Coarse

13 fraction particles had little association with evening peak flow. Tiittanen et al. (1999) also

14 reported a significant effect of $PM_{10-2.5}$ for cough. Thus, cough may be an appropriate outcome

15 related to coarse fraction particle effects. However, the limited data base suggests that further

16 study is appropriate. The report by Zhang, et al. (2000) of an association between coarse fraction

17 particles and the indicator "runny nose" is noted also.

18   Published epidemiological studies have collectively indicated that exposure to PM air

19 pollution can be associated with adverse human health effects, and that asthmatics represent a

20 population that can be especially affected by acute exposures to air pollution (e.g., see Koren and

21 Utell, 1997). In particular, prospective epidemiologic studies of panels of individuals confirm

22 the air pollution-asthma exacerbation association.

23   For respiratory symptoms and PFT changes, several new asthma studies report relationships

24 with ambient PM measures. The peak flow analyses results for asthmatics tend to show small

25 decrements for both PM_{10} and $PM_{2.5}$. Several studies included $PM_{2.5}$ and PM_{10} independently in

26 their analyses of peak flow. Of these, Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et

27 al. (1997), and Romieu et al. (1996) all found comparable results for $PM_{2.5}$ and PM_{10}. The study

28 of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas

29 (2000) found larger effects for $PM_{2.5}$ than for coarse fraction particles. Three studies included

30 both PM_{10} and $PM_{2.5}$ in their analyses of respiratory symptoms. The studies of Peters et al.

31 (1997c) and Tiittanen et al. (1999) found similar effects for the two PM measures. Only the

1   Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$. While the PM associations

2   with adverse health effects among asthmatics and others are well documented, the type/source(s)

3   of those particles most associated with adverse health effects among asthmatics are not known at

4   this time. Indeed, the makeup of PM varies greatly from place to place and over time, depending

5   upon factors such as the sources that contribute to the pollution and the prevailing atmospheric

6   conditions, affecting particle formation, coagulation, transformation, and transport. One

7   suspected causal PM agent is the fine particle component of diesel combustion exhaust.

8   Two studies (Delfino et al., 1998; Ostro et al., 2001) examined PM effects on asthmatics

9   using one hour maximum exposure measures by TEOM, and both studies indicate a relationship

10   with measures of respiratory symptoms. Further research is needed at these shorter exposure

11   times for different PM size fractions.

12   For non-asthmatics, several studies evaluated $PM_{2.5}$ effects. Naeher et al. (1999) reported

13   similar AM PEF decrements for both $PM_{2.5}$ and PM_{10}. Neas et al. (1996) reported a

14   nonsignificant negative association for PEF and $PM_{2.1}$, and Neas et al. (1999) also reported

15   negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significantly PM

16   PEF association with $PM_{2.5}$, and Tiittanen et al. (1999) also reported negative but nonsignificant

17   association for PEF and $PM_{2.5}$. Gold et al. (1999) reported significantly PEF results. Schwartz

18   and Neas (2000) reported significant $PM_{2.5}$ effects relative to lower respiratory symptoms.

19   Tiittanen et al. (1999) showed significant effects for cough and $PM_{2.5}$ for a 4-day average.

20   Another study conducted by Peters et al. (1997c) in Erfurt, Germany in 1992 is unique for

21   two reasons: (1) they studied the size distribution in the range 0.01 to 2.5 μm and (2) examined

22   the number of particles. They report that the health effects of 5 day means of the number count

23   (NC) for ultrafine particles were larger than those related to the mass of the fine particles. For

24   NC 0.01 - 0.1, cough was significant for the same day and the five day mean.

25   In a chronic respiratory disease study of 22-24 North American communities evaluated in

26   the 1996 PM AQCD, Raizenne et al. (1996) found $PM_{2.1}$ to be related to a statistically significant

27   FVC deficit of -3.21% (-4.98, -1.41). Dockery et al. (1996) also reported $PM_{2.1}$ associations

28   with increased bronchitis; odds ratio = 1.50 (95% CI = 0.91, 2.47).

29   The above new studies offer much more information than was available in 1996. Effects

30   were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory

31   hospital admissions and cough. Still insufficient data exists from these relatively limited studies

1   to allow strong conclusions at this time as to which size-related ambient PM components may be

2   most strongly related to one or another morbidity endpoints. Very preliminarily, however, fine

3   particles appear to be more strongly implicated in cardiovascular outcomes than are coarse

4   fraction particles, whereas both seem to impact respiratory endpoints.

5

8.4.4 The Question of Lags

7   The effect of selecting lags on the resulting model for PM health effects is one of the main

8   issues in model selection. Using simulated data with parameters similar to a Seattle PM_{10-25} data

9   series, Lumley and Sheppard (2000) showed that the bias resulting from the selection is shown to

10   be similar in size to the relative risk estimates from the measured data. More precisely, the log

11   relative risk from the measured Seattle data is about twice the mean bias in the simulated control

12   data, and the published estimate of relative risk is only at the 90th percentile of the bias

13   distribution in these control analysis. The selection rule used was to choose the lag (between

14   0 and 6 day) with the largest estimated relative risk. In comparisons to real data from Seattle for

15   other years and from Portland, OR (with similar weather patterns to Seattle), similar bias issues

16   became evident.

17   In most of the past air pollution health effects time-series studies, after the basic model (the

18   best model with weather and seasonal cycles as covariates) was developed, several pollution lags

19   (usually 0 to 3 or 4 days) were individually introduced and the most significant lag(s) chosen for

20   the RR calculation. While this practice may bias the chance of finding a significant association,

21   without a firm biological reason to establish a fixed pre-determined lag, it appears reasonable.

22   Due to likely individual variability in response to air pollution, the apparent lags of effects

23   observed for aggregated population counts are expected to be "distributed" (i.e., symmetric or

24   skewed bell-shape). The "most significant lag" in such distributed lags is also expected to

25   fluctuate statistically. The "vote-counting" of the most significant lags reported in the past

26   PM-mortality studies shows that 0 and 1 day lags are, in that order, the most frequently reported

27   "optimal" lags, but such estimates may be biased because these lags are also likely the most

28   frequently examined ones. Thus, a more systematic approach across different data sets was

29   needed to investigate this issue.

30   The Samet et al. (2000b) analysis of the 90 largest U.S. cities provides particularly useful

31   information on this matter. Figure 8-28 depicts the Samet et al. (2000b) overall pooled results,
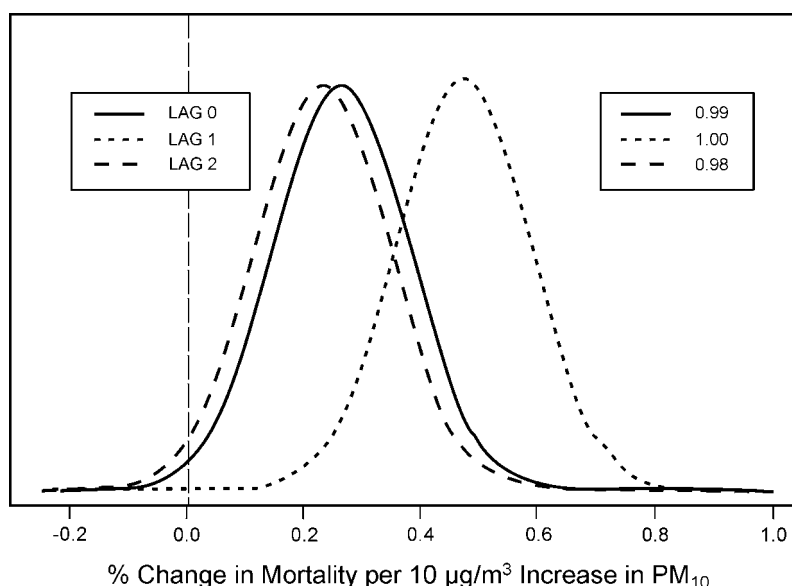
Figure 8-28. Marginal posterior distribution for effects of PM_{10} on all cause mortality at lag 0, 1, and 2 for the 90 cities. From Samet et al. (2000a,b). The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

Source: Samet et al. (2000b).

1   showing the posterior distribution of PM_{10} effects for the 90 cities for lag 0, 1, and 2 days. It can

2   be seen that the effect size estimate for lag 1day is about twice that for lag 0 or lag 2 days,

3   although their distributions overlap. However, a careful examination of Figures 6 and 7 in the

4   NMMAPS I Report suggests that the maximum PM_{10} effect may occur in different cities with

5   somewhat different lag relationships. In terms of the magnitude of the estimated PM_{10} effects,

6   Table 8-40, based on NMMAPS I Figure 7 (posterior bivariate distribution for each county; PM_{10}

7   effect adjusted for O_3), suggests that somewhat different patterns may apply in different

8   locations. These data suggest that while lag 1 effects are typically the largest, there may be some

9   situations in which lag 0 or lag 2 effects are larger.

10   The NMMAPS mortality and morbidity analyses and another HEI-sponsored study on PM

11   components (Lippmann et al., 2000) illustrate three different ways to deal with temporal

12   structure: (1) assume all sites have the same lag, e.g., 1 day, for a given effect; (2) use the lag or

TABLE 8-40. COMPARISON OF PM$_{10}$ EFFECT SIZES ESTIMATED BY NMMAPS ANALYSES FOR 0, 1, AND 2 DAY LAGS FOR THE 20 LARGEST U.S. CITIES

County	Ordered PM$_{10}$ effect sizes
Los Angeles	Lag 0 < lag 1 << lag 2
New York	Lag 0 = lag 1 >> lag 2
Chicago	Unreadable
Dallas/Fort Worth	Lag 0 > lag 1, lag 1 < lag 2
Houston	Lag 0 < lag 1, lag 1 > lag 2
San Diego	Lag 0 = lag 1 > lag 2
Santa Ana /Anaheim	Lag 0 > lag 1 > lag 2
Phoenix	Lag 0 = lag 1 < lag 2
Detroit	Lag 0 < lag 1, lag 1 > lag 2
Miami	Lag 0 < lag 1 = lag 2
Philadelphia	Lag 0 < lag 1, lag 1 > lag 2
Seattle	Lag 0 < lag 1, lag 1 > lag 2
San Jose	Lag 0 > lag 1 = lag 2
Cleveland	Lag 0 > lag 1, lag 1 < lag 2
San Bernardino	Lag 0 > lag 1 = lag 2
Pittsburgh	Lag 0 < lag 1, lag 1 > lag 2
Oakland	Lag 0 < lag 1 = lag 2
San Antonio	Lag 0 = lag 1 < lag 2
Riverside	Lag 0 < lag 1, lag 1 > lag 2

1   moving average giving the largest or most significant effect and for each pollutant and endpoint;

2   and (3) use a flexible distributed lag model, with parameters adjusted to each site

3   The NMMAPS mortality analyses used the first approach. This approach introduces a

4   consistent response model across all locations. However, since the cardiovascular, respiratory, or

5   other causes of acute mortality usually associated with PM are not at all specific, there is little

6   *a priori* reason to believe that they must have the same relation to current or previous PM

7   exposures at different sites. The imposed consistency in lag that maximizes the aggregate effect

1   of lag 1 across all cities, in Figure 15-18 and 24 of NMMAPS II, may obscure important regional

2   or local differences for lags other than 1 day. Moolgavkar (2000a,b) illustrates this point for

3   three large U.S. cities where strong PM effects on cardiovascular mortality occur at lags 4-5 and

4   1-2 days in Maricopa County, lag 3 in Cook County, and lag 0 in Los Angeles County. These

5   may correspond to the onset or exacerbation of different illnesses leading to cardiovascular

6   mortality.

7   The NMMAPS morbidity studies evaluate 0- and 1-day lags, the moving average of 0 and

8   1-day lags, polynomial distributed lag models, and unrestricted distributed lag models. The

9   first-stage models for each city in the study were fitted for each city, with no restriction as to a

10   consistent model across all cities, and combined across all 14 cities in the second stage as shown

11   in Table 14 and Figure 23 of NMMAPS II. A comparison of the data tabulated in the NMMAPS

12   Report Appendices shows large differences across cities in the apparent magnitude of the PM_{10}

13   effect, depending on how the PM concentration data over the preceding few days are used.

14   The approach used in Lippmann et al. (2000) and many other studies is to use the model

15   that maximizes some global model goodness-of-fit criterion. This leads to selection of different

16   models at different sites, as might be expected. However, the best-fitting model (for lags, for

17   example) is often the model with the largest or most significant PM_{10} coefficient. All models for

18   the pollutant(s) of interest are usually compared among themselves only after a preliminary

19   baseline model has been fitted. The baseline model takes into account most of the other

20   variables with which PM_{10} could be plausibly associated, so that the remaining variation in

21   morbidity or mortality that can be explained by including PM_{10} indicators with different temporal

22   structures is nearly "orthogonal" or independent of the baseline model. The restriction to the

23   same lag day at all sites certainly increases the precision of that estimate, but possibly at the cost

24   of obscuring different relationships between time of exposure and health effect at other sites.

25   An additional complication in assessing the shape of a distributed lag is that the apparent

26   spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e.,

27   episodes may persist for a few days), which may vary from city to city and from pollutant to

28   pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and

29   may tend to obscure important nuances of lag structures that may provide important clues to

30   possible different lags between PM exposures and different cause-specific effects.

1   Thus, it is possible that the extent of lag and its spread may vary depending on the cause of

2   death. For example, Rossi et al. (1999) report that, in their analysis of TSP-cause specific

3   mortality in Milan, Italy, the lags varied for different cause of death (i.e., same day for respiratory

4   infections and heart failure; 3-4 days for myocardial infarction and COPD). Thus, the lag for

5   total mortality may exhibit mixed lags (weighted by the frequency of deaths in each cause).

6   Another example was reported for a recent Mexico City study (Borja-Aburto et al., 1998), in

7   which they found significant $PM_{2.5}$-total mortality associations for same day and 4-day lag, but

8   not for the intervening 2 to 3 days (percent increases per 25 $\mu g/m^3$ were 3.38, −4.00, 1.03,

9   1.08,3.43, 2.49, for 0 through 5 day lags, respectively). The authors state: "This phenomenon is

10   consistent with both a harvesting of highly susceptible persons on the day of exposure to high

11   pollution levels and a lagged increase in mortality due to delayed effects of reduction of

12   pulmonary defenses, cardiovascular complications, or other homeostatic changes among

13   less-compromised individuals". It is interesting to note that Wichmann et al. (2000) also

14   reported that the most predictive single day effects on mortality for mass concentrations of

15   0.01-2.5 μ particles were either immediate (0-1 d lag) or delayed (4-5 d lag) for their data from

16   Erfurt, Germany.

17   It should also be noted that if one chooses the most significant single lag day only, and if

18   more than one lag day shows positive (significant or otherwise) associations with mortality, then

19   reporting a RR for only one lag would also underestimate the pollution effects. Schwartz

20   (2000b) investigated this issue, using the 10 U.S. cities data where daily PM_{10} values were

21   available for 1986-1993. Daily total (non-accidental) deaths of persons 65 years of age and older

22   were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint,

23   barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were

24   examined using four models: 1-day mean at lag 0 day; 2-day mean at lag 0 and 1 day; second-

25   degree distributed lag model using lags 0 through 5 days; unconstrained distributed lag model

26   using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates

27   were used to combine results. The results indicated that the effect size estimates for the

28   quadratic distributed model and unconstrained distributed lag model were similar. Both

29   distributed lag models resulted in substantially larger effect size estimates (7.25% and 6.62%,

30   respectively, as percent excess total death per 50 $\mu g/m^3$ increase in PM_{10}) than the single day lag

31   (3.29%) and moderately larger effect size estimates than the two-day average models (5.36%).

1   Samet et al. (2000a,b) also applied 7- and 14-day unconstrained distributed lag models to

2   Chicago, Minneapolis/St. Paul, and Pittsburgh data, and reported that the sum of the 7-day

3   distributed lag coefficients was greater than the estimates based on a single day's value, but the

4   14-day estimate was substantially lower than the 7-day estimate in Chicago and Minneapolis/

5   St. Paul. Thus, it is possible that the usual RR estimate using one lag day may underestimate PM

6   effects.

7   Mis-specification of the lag structure may cause important modeling biases. Most of the

8   published literature for the U.S. evaluates only single-day models, a choice dictated by the every-

9   sixth-day sampling schedule used for PM_{10} in many U.S. cities. When this occurs, it is not

10   possible to evaluate multi-day models with greater biological plausibility, such as moving

11   average models and distributed lag models. Only three of the 20 largest U.S. cities used in the

12   NMMAPS mortality study (Chicago, Minneapolis-St. Paul, Pittsburgh) had daily data (Samet

13   et al., 2000a,b,c). The 14 cities used in the NMMAPS hospital admissions study had daily PM_{10}

14   data, but some of these cities were too small to be included among the 90 largest cities in the

15   mortality study (Canton and Youngstown, OH, Boulder and Colorado Springs, CO). An every-

16   other-day sampling schedule was used in the Harvard Six City Study, for which the PM data on a

17   given day has been used as though it were a two-day moving, alternately concurrent with

18   mortality on half the days and lagging mortality by one day on the other days. While the most

19   commonly used lags in PM time series models are zero or one day, some studies have found PM

20   effects with longer lags (Loomis et al., 1999, in Mexico City; Ponka et al., 1999, for Helsinki),

21   and other studies have found effects at both short and long time lags in some cities (Moolgavkar,

22   2000a,b). It is therefore plausible that mortality or hospital admissions from PM may arise from

23   different responses or PM-associated diseases with different characteristic lags, for example, that

24   cardiovascular responses may arise almost immediately after exposure, within zero or one days

25   or even within two hours (Peter et al., 2002, for myocardial infarction).

26   One would then expect to see different best-fitting lags for different cause-specific

27   mortality or hospital admissions. This idea was fully demonstrated in Lippmann et al. (2000)

28   where different single-day lag models for different health endpoints, PM metrics, and gaseous

29   pollutants were included in the model. The best-fitting PM models had lag 0 to 3 days,

30   depending on the endpoint. This problem is not solved by use of distributed lag models.

31   Schwartz and Zanobetti (2002) found it necessary to use different distributed lag models in each

of the 10 cities whose concentration-response functions were combined by meta-smoothing. One

wonders if the meta-smoothing results by region (Dominici et al., 2002) might have been

changed if the concentration-response function and optimal lag for each city had been used.

In this case, model mis-specification may involve a combination of two potential biases.

8.4.5 New Assessments of Mortality Displacement

There have been a few studies that investigated the question of "harvesting", a phenomenon

in which a deficit in mortality occurs following days with (pollution-caused) elevated mortality,

due to depletion of the susceptible population pool. This issue is very important in interpreting

the public health implication of the reported short-term PM mortality effects. The 1996 PM

AQCD discussed suggestive evidence observed by Spix et al. (1993) during a period when air

pollution levels were relatively high. Recent studies, however, generally typically used data from

areas with lower, non-episodic pollution levels.

Schwartz (2000c) separated time-series air pollution, weather, and mortality data from

Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) "intermediate"

fluctuations; (3) "short-term" fluctuations. By varying the cut-off between the intermediate and

short term, evidence of harvesting was sought. The idea is, for example, if the extent of

harvesting were a matter of a few days, associations between weekly average values of mortality

and air pollution (controlling for seasonal cycles) would not be seen. For COPD, Schwartz

(2000c) reported evidence indicating that most of the mortality was only displaced by a few

weeks; for pneumonia, heart attacks, and all cause mortality, the effect size increased as longer

time scales were included. The percent increase in deaths associated with a 25 μg/m^3 increase in

PM$_{2.5}$ increased from 5.3% (95%CI: 6.8, 9.0) to 9.64% (95%CI: 8.2, 11.1).

Schwartz and Zanobetti (2000) used the same approach described above to analyze a larger

data set from Chicago, IL for 1988-1993. Total (non-accidental), in-hospital, out-of-hospital

deaths, as well as heart disease, COPD, and pneumonia elderly hospital admissions were

analyzed to investigate possible PM$_{10}$ "harvesting" effects. GAM Poisson models adjusting for

temperature, relative humidity, day-of-week, and season were applied in baseline models using

the average of the same day and previous day's PM$_{10}$. Seasonal and trend decomposition

techniques called STL were applied to the health outcome and exposure data to decompose them

into different time-scales (i.e., short-term to long-term), excluding long seasonal cycles (120 day

window). The associations were examined with smoothing windows of 15, 30, 45, and 60 days. The effect size estimate for deaths outside hospital was larger than for deaths inside hospital. All cause mortality showed an increase in effect size at longer time scales. The effect size for deaths outside hospital increases more steeply with increasing time scale than that for inside hospital deaths.

Zanobetti et al. (2000b) used GAM distributed lag models to help quantify mortality displacement in Milan, Italy, 1980-1989. Non-accidental total deaths were regressed on smooth functions of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect. TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.

Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for PM regression coefficients (i.e., mortality relative risk) as observed in frequency domain. Three levels of harvesting, 3 days, 30 days, and 300 days were simulated. As expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the real data from Philadelphia, the regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger suggested that "harvesting-resistant" regression coefficients could be obtained by excluding the coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of those coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, except perhaps the spectral analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients

1   by frequency (*gain*) may be useful in evaluating the potentially frequency-dependent

2   relationships among multiple time series. A few past examples in air pollution health effects

3   studies include: (1) Shumway et al.'s (1983) analysis of London mortality analysis, in which

4   they observed that significant coherence occurred beyond two week periodicity (they interpreted

5   this as "pollution has to persist to affect mortality"); (2) Shumway et al.'s (1988) analysis of

6   Los Angeles mortality data, in which they also found larger coherence in the lower frequency;

7   (3) Ito's (1990) analysis of London mortality data in which he observed relatively constant gain

8   (regression coefficient) for pollutants across the frequency range, except the annual cycle. These

9   results also suggest that associations and effect size, at least, are not concentrated in the very high

10   frequency range.

11   Schwartz (2000c), Zanobetti et al. (2000b), and Zeger et al.'s (1999) results all suggest that

12   the extent of harvesting, if any, is not a matter of only a few days. Other past studies that used

13   frequency domain analyses are also at least qualitatively in agreement with the evidence against

14   the short-term only harvesting. Since very long wave cycles (> 6 months) need to be controlled

15   in time-series analyses to avoid seasonal confounding, the extent of harvesting beyond 6 months

16   periodicity is not possible in time-series study design. While these studies suggest that observed

17   short-term associations are not simply due to short-term harvesting, more data are needed to

18   obtain quantitative estimates of the extent of prematurity of deaths.

19

20   **8.4.6 Concentration-Response Relationships for Ambient PM**

21   In the 1996 PM AQCD, the limitations of identifying 'threshold' in the concentration-

22   response relationships in observational studies were discussed including the low data density in

23   the lower PM concentration range, the small number of quantile indicators often used, and the

24   possible influence of measurement error. Also, a threshold for a population, as opposed to a

25   threshold for an individual, has some conceptual issues that need to be noted. For example,

26   Schwartz (1999) discussed that, since individual thresholds would vary from person to person

27   due to individual differences in genetic level susceptibility and pre-existing disease conditions, it

28   would be almost mathematically impossible for a threshold to exist in the population. This

29   argument holds only if the most sensitive members of a population are sensitive to very low

30   concentrations, which may not be the case.   The person-to-person difference in the relationship

31   between personal exposure and the concentration observed at a monitor would also add to the

1   variability. Because one cannot directly measure but can only compute or estimate a population

2   threshold, it would be difficult to interpret an observed threshold, if any, biologically. Despite

3   these issues, several studies have attempted to address the question of threshold by analyzing

4   large databases, or by conducting simulations.

5   Daniels et al. (2000) examined the presence of threshold using the largest 20 U.S. cities for

6   1987-1994. The authors compared three log-linear GAM regression models: (1) using a linear

7   PM_{10} term; (2) using a cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding

8   approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with

9   a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. The covariates

10   included in these models are similar to those used by the same research group previously (Kelsall

11   et al., 1997; Samet et al., 2000a,b), including the smoothing function of time, temperature and

12   dewpoint, and day-of-week indicators. Total, cardiorespiratory, and other mortality series were

13   analyzed. These models were fit for each city separately, and for model (1) and (2), the

14   combined estimates across cities were obtained by using inverse variance weighting if there was

15   no heterogeneity across cities, or by using a two-level hierarchical model if there was

16   heterogeneity. The best fit among the models, within each city and over all cities, were also

17   determined using the Akaike's Information Criterion (AIC). The results using the spline model

18   showed that, for total and cardiorespiratory mortality, the spline curves were roughly linear,

19   consistent with the lack of a threshold. For mortality from other causes, however, the curve did

20   not increase until PM_{10} concentrations exceeded 50 $\mu g/m^3$. While the test of heterogeneity

21   indicated that there was considerable heterogeneity in these curves across cities (see Figure

22   8-29), the shapes of the curves were similar across cities, with no indication of one city unduly

23   influencing the overall estimate of the curves. The hypothesis of linearity was examined by

24   comparing the AIC values across models. The results suggested that the linear model was

25   preferred over the spline and the threshold models. Thus, these results suggest that linear models

26   without a threshold may well be appropriate for estimating the effects of PM_{10} on the types of

27   mortality of main interest.

28   Thus, while these studies do not refute the usual assumption of a linear no-threshold

29   concentration-response function, neither do they provide unqualified support for that assumption.

30   Sensitivity analyses for individual city studies' concentration-response function would be

31   helpful. Schwartz and Zanobetti (2000) investigated the presence of threshold by simulation and
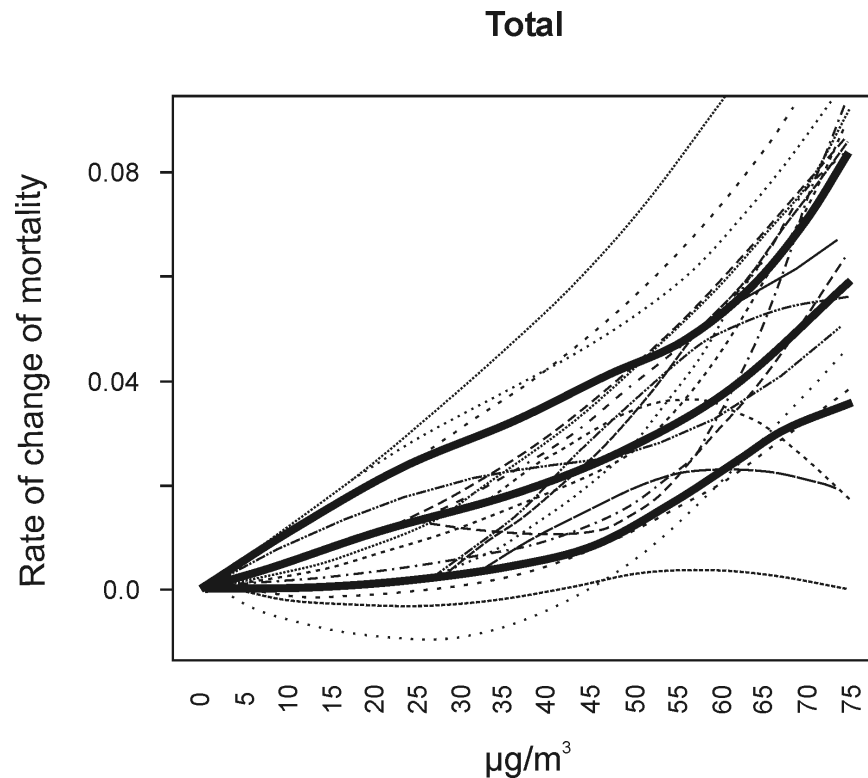
Total

Figure 8-29. **Particulate matter <10 μm in aerodynamic diameter (PM$_{10}$)-total mortality dose-response curve for the mean lag PM$_{10}$ and 95% credible regions (solid lines), 20 largest U.S. cities, 1987-1994. Dashed lines denote the Bayesian estimates of the city-specific dose-response curves.**

Source: Daniels et al. (2000).

1   actual data analysis of 10 U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL;

2   Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO;

3   Spokane, WA; and Seattle, WA, where daily PM$_{10}$ were available for years 1986-1993. First, a

4   simulation was conducted to show that the combining smoothed curves across cities (the authors

5   called this approach "meta-smoothing") could produce estimates of a mean unbiased exposure-

6   esponse curve. Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were

7   used to generate mortality series in the 10 cities, and GAM Poisson models were used to estimate

8   respective exposure-response curves. Effects of measurement errors were also simulated. In the

9   analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature,

10   dewpoint, and barometric pressure, and day-of-week. Smooth function of PM$_{10}$ with the same

1   span (0.7) was used in each of the cities. The predicted values of the log relative risks were

2   computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the

3   predicted values were combined across cities using inverse-variance weighting. The simulation

4   results indicated that the "meta-smoothing" approach did not bias the underlying relationships for

5   the linear and threshold models, but did result in a slight downward bias for the logarithmic

6   model. Measurement error (additive or multiplicative) in the simulations did not cause upward

7   bias in the relationship below threshold. The threshold detection in the simulation was not very

8   sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the

9   combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.

10   Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time

11   series studies. Based on the realistic range of error observed from actual Toronto pollution data

12   (average site-to-site correlation: 0.90 for O_3; 0.76 for COH; 0.69 for TSP; 0.59 for SO_2; 0.58 for

13   NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of

14   exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were

15   generated with three PM_{10} threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$). LOESS

16   with a 60% span was used to observe the exposure-response curves for these 18 combinations of

17   exposure-response relationships with error. A parameter threshold model was also fit using non-

18   linear least squares. Graphical presentations indicate that LOESS adequately detects threshold

19   under no error, but the thresholds were "smoothed out" under the extreme error scenario. Use of

20   a parametric threshold model was adequate to give "nearly unbiased" estimates of threshold

21   concentrations even under the conditions of extreme measurement error, but the uncertainty in

22   the threshold estimates increased with the degree of error. They concluded, "if threshold exists,

23   it is highly likely that standard statistical analysis can detect it".

24   The Smith et al. (2000) study of associations between daily total mortality and $PM_{2.5}$ and

25    $PM_{10-2.5}$ in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold.

26   In the linear model, the authors found that mortality was significantly associated with $PM_{10-2.5}$,

27   but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model

28   in which several possible thresholds were specified; and (2) a B-spline (spline with cubic

29   polynomials) model with 4 knots. Using the piecewise model, there was no indication that there

30   was a threshold for $PM_{10-2.5}$. However, for $PM_{2.5}$, the piecewise model resulted in suggestive

31   evidence for a threshold, around 20 to 25 $\mu g/m^3$. The B-spline results also showed no evidence

1   of threshold for $PM_{10\text{-}2.5}$, but for $PM_{2.5}$, a non-linear curve showed a change in the slope around

2   20 μg/m^3. A further Bayesian analysis for threshold selection suggested a clear peak in the

3   posterior density of $PM_{2.5}$ effects around 22 μg/m^3. These results, if they in fact reflect reality,

4   make it difficult to evaluate the relative roles of different PM components (in this case, $PM_{2.5}$

5   versus $PM_{10\text{-}2.5}$). However, the concentration-response curve for $PM_{2.5}$ presented in this

6   publication suggests more of a U- or V-shaped relationship than the usual "hockey stick"

7   relationship. Such a relationship is, unlike the temperature-mortality relationship, difficult to

8   interpret biologically. Because the sample size of this data ($\approx$3 years) is relatively small, further

9   investigation of this issue using similar methods but a larger data set is warranted. Other studies

10 evaluate non-linear relationships using a multi-city meta-smoothing approach based on non- or

11 semi-parametric smoothers rather than on linear parametric models.

12   Many ad hoc decisions go into model selection in air pollution health effects studies. The

13 effect of some of these decisions on relative risk estimates for Birmingham, AL, PM_{10} data,

14 previously analyzed by Schwartz (1993) and others, is illustrated by Smith et al. (2000). The

15 response variable is non-accidental mortality. Specifically, the selection of meteorological

16 variables, the selection of an exposure variable (as a weighted average of lagged PM values), and

17 the possibility of nonlinear effects, such as threshold effects, are investigated. The results are

18 sensitive to the inclusion of humidity in addition to temperature. This inclusion decreases the

19 resulting PM_{10} coefficient. The model is highly sensitive to the definition of an exposure

20 measure. For example, when lags 0-4 were averaged, there was no significant effect. In an

21 attempt to account for a nonlinear PM-mortality effect, there appeared to be little effect of

22 exposure below 80 μg/m^3, and a threshold analysis (as well as a generalized additive models

23 approach) supported the conclusion that the main effect is at higher values of PM. Although this

24 paper was based on an intensive analysis of a single data set (in contrast to other studies, such as

25 NMMAPS analysis, which combined data form many cities), it demonstrated the very wide range

26 of interpretations that are possible using alternative, but statistically valid, analyses of the same

27 data.

28

29

30

8.4.7 New Assessments of Consequences of Measurement Error

8.4.7.1 Theoretical Framework for Assessment of Measurement Error

Since the 1996 PM AQCD, there have been some advances in conceptual framework development to investigate the effects of measurement error on PM health effects estimated in time-series studies. Several new studies evaluated the extent of bias caused by measurement errors under a number of scenarios with varying extent of error variance and covariance structure between co-pollutants.

Zidek et al. (1996) investigated, through simulation, the joint effects of multi-collinearity and measurement error in Poisson regression model, with two covariates with varying extent of relative errors and correlation. Their error model was of classical error form (W=X+U, where W and X are surrogate and true measurements, respectively, and the error U is normally distributed). The results illustrated the transfer of effects from the "causal" variable to the confounder. However, for the confounder to have larger coefficients than the true predictor, the correlation between the two covariates had to be large ($r = 0.9$), with moderate error ($\sigma > 0.5$) for the true predictor, and no error for the confounder in their scenarios. The transfer-of-causality effect was mitigated when the confounder also became subject to error. Another interesting finding that Zidek et al. reported is the behavior of the standard errors of these coefficients: when the correlation between the covariates was high ($r = 0.9$) and both covariates had no error, the standard errors for both coefficients were inflated by factor of 2; however, this phenomenon disappeared when the confounder had error. Thus, multi-collinearity influences the significance of the coefficient of the causal variable only when the confounder is accurately measured.

Zeger et al. (2000) also conducted a mathematical analysis of PM mortality effects in ordinary least square model (OLS) with the classical error model, under varying extent of error variance and correlation between two predictor variables. The error described here was analytical error (e.g., discrepancy between the co-located monitors). In general, they found that positive regression coefficients are only attenuated, but null predictors (zero coefficient) or weak predictors are only able to appear stronger than true positive predictors under unusual conditions: (1) true predictors must have very large positive or negative correlation (i.e., $|r| > 0.9$); (2) measurement error must be substantial (i.e., error variance $\approx$ signal variance); and (3) measurement errors must have a large negative correlation. They concluded that estimated

1   FP health effects are likely underestimated, although the magnitude of bias due to the analytical

2   measurement error is not very large.

3   Zeger et al. (1999) illustrated the implication of the classical error model and the Berkson

4   error model (i.e., $X = W + U$) in the context of time-series study design. Their simulation of the

5   classical error model with two predictors, with various combinations of error variance and

6   correlation between the predictors/error terms, showed results similar to those reported by Zidek

7   et al. (1996). Most notably, for the transfer of the effects of one variable to the other (i.e., error-

8   induced confounding) to be large, the two predictors or their errors need to be substantially

9   correlated. Also, for the spurious association of a null predictor to be more significant than the

10   true predictor, their measurement errors have to be extremely negatively correlated—a condition

11   not yet demonstrated as occurring in actual air pollution data sets.

12   Zeger et al. also laid out a comprehensive framework for evaluating the effects of exposure

13   measurement error on estimates of air pollution mortality relative risks in time-series studies.

14   The error, the difference between personal exposure and the central station's measurement of

15   ambient concentration was decomposed into three components: (1) the error due to having

16   aggregate rather than individual exposure; (2) the difference between the average personal

17   exposure and the true ambient concentration level; and, (3) the difference between the true and

18   measured ambient concentration level. By aggregating individual risks to obtain expected

19   number of deaths, they showed that the first component of error (the aggregate rather than

20   individual) is a Berkson error, and, therefore is not a significant contributor to bias in the

21   estimated risk. The second error component is a classical error and can introduce bias if there are

22   short-term associations between indoor source contributions and ambient concentration levels.

23   Recent analysis, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000)

24   and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship

25   between the ambient concentration and the nonambient components of personal exposure to PM.

26   However, a bias can arise due to the difference between the personal exposure to ambient PM

27   (indoors plus outdoors) and the ambient concentration. The third error component is the

28   difference between the true and the measured ambient concentration. According to Zeger et al.

29   the final term is largely of the Berkson type if the average of the available monitors is an

30   unbiased estimate of the true spatially averaged ambient level.

1   Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to

2   estimate the second error component and its influence on estimated risks. The correlation

3   coefficient between the error (the average population PM_{10} total exposure minus the ambient

4   PM_{10} concentration) and the ambient PM_{10} concentration was estimated to be -0.63. Since this

5   correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the

6   regression of mortality on z_t, the daily ambient concentration) will tend to underestimate the

7   coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on $\bar{x}_t$, the daily average total

8   personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then proceed to assess the

9   size of the bias that will result from this exposure misclassification, using daily ambient

10   concentration, z_t. As shown in Equation 9, the daily average total personal exposure, $\bar{x}_t$, can be

11   separated into a variable component, $\theta_1 \, z_t$, dependent on the daily ambient concentration, z_t, and

12   a constant component, θ_o, independent of the ambient concentration.

13

14                              $$\bar{x}_t = \theta_0 + \theta_1 z_t + \varepsilon_t \tag{8-5}$$

15   where ε_t is an error term.

16   If the nonambient component of the total personal exposure is independent of the ambient

17   concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the

18   regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott

19   et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the

20   total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to

21   the ambient concentration. (The ambient component of personal exposure includes exposure to

22   ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated

23   indoors.) In this well-known approach to adjust for exposure measurement error, called

24   regression calibration (Carroll et al., 1995), the estimate of β_x has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$.

25   Thus, for the regression calibration, the value of β_x (based on the total personal exposure) does

26   not depend on the total personal exposure but is given by β_z, based on the ambient concentration,

27   times θ_1, the ratio of the ambient component of personal exposure to the ambient concentration.

28   A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

29   Zeger et al. (2000) use Equation 9, with $\hat{\theta}_o = 59.95$ and $\theta_1 = 0.60$, estimated from the

30   PTEAM data, to simulate values of daily average personal exposure, x^*_t, from the ambient

1	concentrations, z_t, for PM_{10} in Riverside, CA, 1987-1994. They then compare the mean of the
2	simulated $\hat{\beta}_x$s, obtained by the series of log-linear regressions of mortality on the simulated x^*_t,
3	with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the
4	log-linear regression of mortality directly on z_t. The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$, is very close to
5	$\theta_1 = 0.60$. Dominici et al. (2000) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an
6	estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical
7	model. Their findings were qualitatively similar in that $\hat{\beta}_x$ was close to $\hat{\beta}_z / \theta_1$. Thus, it appears
8	that the bias is very close to θ_1 which depends not on the total personal exposure but only on the
9	ratio of the ambient component of personal exposure to the ambient concentration.
10	Zeger et al. (2000), in the analyses described above, also suggested that the error due to the
11	difference between the average personal exposure and the ambient level (the second error type
12	described above) is likely the largest source of bias in estimated relative risk. This suggestion at
13	least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type
14	of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed
15	relatively high site-to-site correlation ($\approx$0.6-0.9), a similar extent of site-to-site correlation for
16	other pollutants is not necessarily expected. Ito et al. (1998) estimated site-to-site correlations
17	(after adjusted for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint
18	temperature, and relative humidity, using multiple stations' data from seven central and eastern
19	states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles,
20	these variables could be categorized into three groups in terms of the extent of correlation:
21	weather variables ($r > 0.9$); O_3, PM_{10}, NO_2 (r: 0.6 - 0.8); CO and SO_2 ($r < 0.5$). These results
22	suggest that the contribution from the third component of error, as described in Zeger et al.
23	(2000), would vary among pollution and weather variables. Furthermore, the contribution from
24	the second component of error would also vary among pollutants; i.e., the ratio of ambient
25	exposure to ambient concentration, called the attenuation coefficient, is expected to be different
26	for each pollutant. Some of the ongoing studies are expected to shed some light on this issue.
27	However, more information is needed on attenuation coefficients for a variety of pollutants.
28	With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999),
29	show reasonably good correlation ($r = 0.6$ to 0.9) between ambient PM concentrations and
30	average population PM exposure, lending support for the use of ambient data as a surrogate for
31	personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore,

1   fine particles are expected to show even better site-to-site correlation than PM_{10}. Wilson and Suh

2   (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and

3   St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for $PM_{10-2.5}$

4   ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-wide

5   exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger

6   mortality associations for fine particles than coarse particles found in the Schwartz et al. (1996a)

7   study may be due in part to larger measurement error for coarse particles.

8   However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle

9   association with mortality is a "false positive", but rather, whether the weaker mortality

10   association with coarse particles is a "false negative". Carrothers and Evans (2000) also

11   investigated the joint effects of correlation and relative error, but they specifically addressed the

12   issue of fine (FP) vs. coarse particle (CP) effect, by assuming three levels of relative toxicity of

13   fine versus coarse particles ($\beta_{FP} / \beta_{CP} = 1, 3,$ and 10) and, then, evaluating the bias, ($B = \{E[\beta_{F'}]/$

14    $E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and

15   CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e.,

16   B=1) as long as FP and CP are measured with equal precision, but, if, for example, FP is

17   measured more precisely than CP, then FP will appear to be more toxic than CP (i.e., $B > 1$);

18   (2) when FP is more toxic than CP (i.e., $\beta_{FP} / \beta_{CP} = 3$ and 10), however, the equal precision of FP

19   and CP results in downward bias of FP ($B < 1$), implying a relative overestimation of the less

20   toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more

21   so as the correlation between FP and CP increases. They also applied this model to real data

22   from the Harvard Six Cities Study, in particular, the data from Boston and Knoxville. Estimation

23   of spatial variability for Boston was based on external data and a range of spatial variability for

24   Knoxville (since there was no spatial data available for this city). For Boston, where the

25   estimated FP-CP correlation was low ($r = 0.28$), estimated error was smaller for FP than for CP

26   (0.85 vs. 0.65, as correlation between true vs. error-added series), and the observed FP to CP

27   coefficient ratio was high (11), the calculated FP to CP coefficient ratio was even larger (26)-thus

28   providing evidence against the hypothesis that FP is absorbing some of the coefficient of CP.

29   For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than

30   for CP (0.9 vs. 0.75), and the observed FP to CP coefficient ratio was 1.4, the calculated true FP

31   to CP coefficient ratio was smaller (0.9) than the observed value, indicating that the coefficient

1 was overestimated for the better-measured FP, while the coefficient was underestimated for the

2 worse-measured CP. Since the amount (and the direction) of bias depended on several variables

3 (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true

4 ratio of the FP toxicity to CP toxicity), the authors concluded "...for instance, it is inadequate to

5 state that differences in measurement error among fine and coarse particles will lead to false

6 negative findings for coarse particles".

7 Fung and Krewski (1999) conducted a simulation study of measurement error adjustment

8 methods for Poisson models, using scenarios similar to those used in the simulation studies that

9 investigated implication of joint effects of correlated covariates with measurement error. The

10 measurement error adjustment methods employed were the Regression Calibration (RCAL)

11 method (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and

12 Stefanski, 1994). Briefly, RCAL algorithm consists of: (1) estimation of the regression of X on

13 W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by

14 its estimate from (1), and conducting the standard analysis (i.e., regression); and (3) adjustment

15 of the resulting standard error of coefficient to account for the calibration modeling. SIMEX

16 algorithm consists of: (1) addition of successively larger amount of error to the original data;

17 (2) obtaining naive regression coefficients for each of the error added data sets; and, (3) back

18 extrapolation of the obtained coefficients to the error-free case using a quadratic or other

19 function. Fung and Krewski examined the cases for: (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$;

20 $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$., all with varying level of correlation (-0.8 to 0.8) with and

21 without classical additive error, and also considering Berkson type error. The behaviors of naive

22 estimates were essentially similar to other simulation studies. In most cases with the classical

23 error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation

24 was small), recovering underlying coefficients. In the presence of Berkson type error, however,

25 even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5).

26 This is the first study to examine the performance of available error adjustment methods that can

27 be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX.

28 Possible reasons why RCAL performed better than SIMEX in these scenarios were not discussed,

29 nor are they clear from the information given in the publication. There has not been a study to

30 apply these error adjustment methods in real time-series health effects studies. These

31 methodologies require either replicate measurements or some knowledge on the nature of error

1   (i.e., distributional properties, correlation, etc.). Since the information regarding the nature of

2   error is still being collected at this time, it may take some time before applications of these

3   methods become practical.

4   Another issue that measurement error may affect is the detection of threshold in time-series

5   studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape

6   of the exposure-response curve, and that such error could make the exposure-response curve to

7   appear linear even when a threshold may exist. However, based on a simulation with realistic

8   range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated that the

9   modern smoothing approach, LOESS, can adequately detect threshold levels ($12.8\ \mu g/m^3$,

10   $24.6\ \mu g/m^3$, and $34.4\ \mu g/m^3$) even with the presence of exposure error (see also Section 8.4.6

11   above).

12   Other issues related to exposure error that have not been investigated include potential

13   differential error among subpopulations. If the exposure errors are different between susceptible

14   population groups (e.g., people with COPD) and the rest of the population, the estimation of bias

15   may need to take such differences into account. Also, the exposure errors may vary from season

16   to season, due to seasonal differences in the use of indoor emission sources and air exchange

17   rates due to air conditioning and heating. This may possibly explain reported season-specific

18   effects of PM and other pollutants. Such season-specific contributions of errors from indoor and

19   outdoor sources are also expected to be different from pollutant to pollutant.

20   In summary, the studies that examined joint effects of correlation and error suggest that PM

21   effects are likely underestimated, and that spurious PM effects (i.e., qualitative bias such as

22   change in the sign of coefficient) due to transferring of effects from other covariates require

23   extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under

24   the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing

25   methods. More data are needed to examine the exposure errors for other pollutants, since their

26   relative error contributions will influence their relative significance in relative risk estimates.

27

28   **8.4.7.2   Spatial Measurement Error Issues That May Affect the Interpretation of**
29   **Multi-Pollutant Models with Gaseous Co-Pollutants**

30   The measurement error framework put forth in Dominici et al. (2000) and Zeger et al.

31   (2000) explicitly assumes that one of the error components has a Berkson error structure.

32   As summarized in (Zeger et al., 2000, p. 421): "This Berkson model is appropriate when z

1　represents a measurable factor [e.g. measured PM or another pollutant] that is shared by a group

2　of participants whose individual [true] exposures x might vary because of time-activity patterns.

3　For example, z might be the spatially averaged ambient level of a pollutant without major indoor

4　sources and x might be the personal exposures that, when averaged across people, match the

5　ambient level." This assumption is likely accurate for sulfates, less so for fine particles and for

6　PM_{10}, and almost certainly incorrect for gases such as CO and NO_2 that may vary substantially on

7　an intra-urban spatial scale with widely distributed local sources.

8　　The usual characterization of longitudinal or temporal pollutant correlation may not

9　adequately characterize the spatial variation that is the more important aspect of association in

10　evaluating possible Berkson errors. Temporal correlation coefficients, even across large

11　distances (e.g. Ito et al., 2000) may be a consequence of large-scale weather patterns affecting the

12　concentrations of many pollutants. Local concentrations for some pollutants with strong local

13　sources and low regional dispersion (especially for CO and NO_2, and $PM_{10-2.5}$ to a lesser extent)

14　may have somewhat smaller temporal correlations and much greater relative spatial variations

15　than PM. Thus, individuals in a large metropolitan area may have roughly similar levels of PM

16　exposure x on any given day for which the ambient average PM concentration z is an adequate

17　surrogate, whatever their space-time activity patterns, residence, or non-residential micro-

18　environments, while the same individuals may be exposed to systematically higher or lower

19　concentrations of a co-pollutant than the spatial average of the co-pollutant. This violates the

20　basic assumption of the Berkson error model that within each stratum of the measured (spatially

21　averaged) level z, the average value of the true concentration x is equal to z, i.e.,

22

23　　　　　　　　　　$$E\{ x \mid z \} = z, \qquad\qquad (8\text{-}6)$$

24

25　where $E\{.\}$ is the average or expected value over the population.

26　　There are empirical reasons to believe that if the strata are chosen to be locations within a

27　metropolitan area, some individuals far from local sources have consistently less exposure than

28　the average ambient concentration (denoted p) for co-pollutants with local sources such as CO

29　and NO_2, and $PM_{2.5}$, whose true exposure (denoted q) depends on the location of the person's

30　residence or other micro-environment where most exposure occurs. For this group,

31

1
$$E\{\, q \mid p \,\} < p, \qquad\qquad\qquad (8\text{-}7)$$

2

3   while others in locations near the local source (such as a busy highway) have systematically

4   higher exposure, so that

5

6
$$E\{\, q \mid p \,\} > p. \qquad\qquad\qquad (8\text{-}8)$$

7

8   There is a substantial and growing body of evidence that adverse health effects are

9   associated with proximity to a major road or highway (Wijst et al., 1994; Monn et al., 2000;

10   Roemer and Hoek, 2001). As shown below, there is good reason to believe that the intra-city

11   variation even in $PM_{2.5}$ is substantial within some U.S. cities. If we assume for the sake of

12   argument that concentrations of PM_{10} or $PM_{2.5}$ are relatively uniformly distributed, then

13   associations of adverse health effects with proximity to a source cannot be attributed to a

14   pollutant such as PM with a uniform spatial distribution. NO_2 is a pollutant often used to

15   illustrate the spatial non-uniformity of the gaseous co-pollutants. Figure 8- from Monn et al.

16   (1997) compares the concentrations of NO_2 and PM_{10} as a function of curbside distance in a

17   moderately busy urban street in Zurich. The PM_{10} concentrations decrease only slightly with

18   increasing distance, with the decrease more likely due to decreasing coarse particle levels than to

19   decreasing fine particle concentrations. The NO_2 concentrations show a much stronger seasonal

20   dependence, decreasing rapidly with increasing distance in the summer and showing little

21   decrease with distance in the winter. However, the belief that $PM_{2.5}$ is spatially uniform should

22   also not be accepted uncritically, as recent analyses for 27 U.S. cities shown in Chapter 3 and

23   Appendix 3A of this document demonstrate.

24   The 90th Percentile differences (P_{90}) between a pair of sites may provide a useful guide to

25   the differences between monitor pairs (and by implication, personal exposure to fine particles)

26   that might be reasonably expected within a metropolitan area. Shown below in Table 8-41 are the

27   maximum, median, and minimum differences between monitor pairs, the monitor pairs at which

28   the largest 90th percentile difference occurs (by reference to the tables in Appendix 3A). Based

29   on these differences, we have shown in Table 8-42 a characterization of cities as "relatively

30   homogeneous" with $P90 < 10\ \mu g/m^3$ and "relatively heterogeneous" if $P90 \geq 10\ \mu g/m^3$. The

31   results in Appendix 3A and Table 8-42 show a variety of spatial patterns of association of $PM_{2.5}$

TABLE 8-41. MAXIMUM, MEDIAN, AND MINIMUM 90ᵗʰ PERCENTILE OF ABSOLUTE VALUES OF DIFFERENCES BETWEEN FINE PARTICLE CONCENTRATIONS AT PAIRS OF MONITORING SITES IN 27 METROPOLITAN AREAS IN ORDER OF DECREASING MAXIMUM DIFFERENCE (based on Chapter 3 and Appendix 3A).

City	N Sites	Maximum	Pair	Median	Minimum
Los Angeles	5	31.0	CE	13.8	11.8
	4 (w/o E) *	20.2	AD	13.7	11.8
Pittsburgh	4	21.3	BD	10.8	4.1
Riverside-San Bernardino	5	20.2	BC	12.6	7.0
Birmingham	5	15.4	AE	10.1	7.5
Seattle	5	15.3	AE	8.2	3.8
	4 (w/o A) *	8.4	CE	7.6	3.8
Gary	4	14.9	BD	8.2	5.9
Cleveland	7	14.9	BG	7.1	3.8
Atlanta	7	14.0	EG	9.4	6.5
	6 (w/o G) *	10.6	CF	8.3	6.5
Detroit	5	13.3	CD	8.6	4.9
Salt Lake C.	6	12.6	AC	7.6	3.9
St. Louis	4	12.5	AD	9.5	6.0
San Diego	4	11.9	CD	10.6	7.4
Louisville	4	11.2	AD	8.7	6.3
Chicago	11	10.5	EK	6.2	3.5
Washington DC	6	10.1	AF	7.4	4.2
	5 (w/o F)	7.7	AD	6.25	4.2
Steubenville	5	9.9	AE	8.45	2.5**
Boise	4	8.9	BD	5.2	3.8
Kansas City	6	7.4	CF	4.1	1.9
Philadelphia	5	6.9	BC	5.2	3.3
Portland OR	4	6.5	AB	4.45	4.0
Grand Rapids	4	6.1	BC	4.8	2.8
Dallas	7	5.6	AE	3.3	2.0
Milwaukee	8	5.5	FH	3.65	2.9
Columbia	4	5.3	AB	3.95	2.7
Tampa	4	5.0	BD	4.45	3.6
Norfolk	5	4.7	AC	3.55	2.6
Baton Rouge	3	3.2	AC	2.9	2.5

* Without one site > 100 km from the others.
** Collocated monitors at sites D and E.

TABLE 8-42. SUMMARY OF WITHIN-CITY HETEROGENEITY BY REGION

Relative Heterogeneity Among Pairs of Monitors			
Relatively Heterogenous		**Relatively Homogeneous**	
East	West	East	West
Atlanta, GA	Los Angeles, CA	Baton Rouge, LA	Boise, ID
Birmingham, AL	Riverside, CA	Columbia, SC	Portland, OR
Chicago, IL	Salt Lake City, UT	Dallas, TX	
Cleveland, OH	San Diego, CA	Grand Rapids, MI	
Detroit, MI		Kansas City, KS-MO	
Gary, IN		Milwaukee, WI	
Louisville, KY		Norfolk, VA	
Pittsburgh, PA		Philadelphia, PA	
St. Louis, MO		Steubenville, OH	
		Tampa, FL	
Washington, DC (with F)	Seattle, WA (with A)	Washington, DC (w/o F)	Seattle, WA (w/o A)

1   within a Metroplitan Statistical Area (MSA). There may be some discernable regional

2   differences; but, because many major population centers are not represented in Appendix 3A,

3   further investigation is likely warranted.

4   The results shown here provide clear evidence that fine particle concentrations may be less

5   homogenous in at least some MSAs than has been previously assumed. This provides support

6   for earlier studies using TSP and PM_{10} cited below. As noted in Chapter 3, these differences may

7   not be strictly related to the distance between monitors, especially where topography plays a role.

8   In many eastern sites, however, particle distribution may be more substantially governed by

9   regional particle concentrations than by local concentrations.

10   A number of recent studies have examined the role of spatial siting of monitors on the

11   estimation of PM effects. Ito et al. (1995) examined the ability of single-site vs. multi-site

12   averages to best estimate total mortality vs. PM_{10} in Cook County (Chicago), IL and Los Angeles

13   County, CA. In order to have a sufficiently large sample size to detect effects, Ito et al. used six

14   PM_{10} sites in Cook County (Chicago), IL and four sites in Los Angeles County, CA.

1 A sinusoidal model was used to account for temporal components, although spline or LOESS

2 methods would now be used. Only one Cook County site had every-day PM samples, and the

3 others as well as the Los Angeles sites had a one-in-six-day sampling schedule. The monitor

4 sites were located in urban and suburban settings, according to the State's objectives. Three of

5 the Los Angeles sites were residential and one was commercial use. One of the Cook County

6 sites was residential, two were commercial, and three were industrial. One of the Chicago sites

7 was intended to monitor population exposure, three to monitor maximum concentrations, and

8 two to monitor both maximum concentrations and personal exposure. There was considerable

9 variation among the distribution of PM_{10} in Cook County (Chicago), IL sites, and among

10 Los Angeles County, CA sites, especially at the upper end of the distribution. The sites were

11 temporally correlated, 0.83 to 0.63 in Cook County, 0.9 to 0.7 in Los Angeles (except for one site

12 pair), across distances of 4 to 26 miles. The Cook County mortality estimates were better

13 estimated by some single-site estimates (Site 2 with everyday data, N = 1251) than by an average

14 using all available data with missing values estimated from non-missing data (N = 1357). The

15 every-six-day subsamples from Site 1 (N = 281) and Site 2 (lag 0, N = 246) were better

16 predictors, and from Site 4 (N = 243) and Site 6 (N = 292) about as good predictors of mortality

17 as the corresponding every-six-day averages (N = 351). In Los Angeles, only Site 4 (N = 349)

18 was about as predictive as the spatial averages (N = 405).

19   Lipfert et al. (2000) examined the relationship between the area in which mortality occurred

20 among residents and the locations of monitoring sites or averages over monitoring sites for

21 several particle size components and particle metrics. The mortality data were located for

22 Philadelphia, PA, for three aditional suburban Philadelphia counties, for Camden, NJ and other

23 New Jersey counties in the Philadelphia - Camden MSA. A single site was used for fine and

24 coarse particles from the Harvard School of Public Health monitors. Additional PA and NJ

25 thoracic particle data were available for 2 to 4 stations and results averaged for at least two

26 stations reporting data. The authors conclude that mortality in any part of the region may be

27 associated with air pollution concentrations or average concentrations in any other part of the

28 region, whether particles or gases. The authors suggest two interpretations: (a) the associations

29 of mortality with pollution were random (from carrying out multiple significance tests) and not

30 causal, or (b) both particles and gaseous pollutants have a broad regional distribution. The

31 authors note that interpretation (b) may lead to large uncertainties in identifying which pollutant

1   exposures for the population are primarily responsible for the observed effects. These data could

2   be studied further to evaluate smaller-scale spatial relationships among health effects and gases.

3   Lippmann et al. (2000) evaluated the effects of monitor siting choice using 14 TSP

4   monitoring stations in Detroit, MI, and nearby Windsor, ON, Canada. The stations operated

5   from 1981-1987 with almost complete data. When a standard log-linear link Poisson regression

6   model for mortality was fitted to TSP data for each of the 14 sites, the relative risk estimates

7   were similar for within-site increments of 5th to 95th percentiles, generally highest and positive at

8   lag day 1, but not statistically significant except for site "w" (site 12, south of the urban center of

9   Wayne County) and nearly significant at sites "f" (west of the city of Detroit), "g" (south of the

10   city) and "v" (suburban site in northwestern Wayne County, MI, generally "upwind" of the

11   urban center). However, as the authors note, all of the reported relative risks are for site-specific

12   increments, which vary by a factor of about 2.5 over the Wayne County - Windsor area. When

13   converted to a common increment of 100 μg/m^3 TSP, the largest excess risks are found when the

14   monitor used in the model is "f" (4.5%), "v" (4.2%), or "w" (3.8%), which also show the most

15   significant effects among the 14 monitors. As the authors note, "... the distributional increments

16   [used] to calculate relative risk tend to standardize the scale of relative risks. This actually makes

17   sense in that if there is a concentration gradient of TSP within a city, and if the various TSP

18   concentrations fluctuate together, then using a site with a low mean TSP for time-series analysis

19   would result in a larger coefficient. This result does warn against extrapolating the effects from

20   one city to an other using a raw regression coefficient [excess relative risk]"

21   Other recent studies also point out other aspects of intra-urban spatial variation in PM

22   concentrations. Kinney et al. (2000) note that in a personal and ambient PM$_{2.5}$ and diesel exhaust

23   particle (DEP) exposure study in a dense urban area of New York City, PM$_{2.5}$ concentrations

24   showed only a moderate site-to-site variation (37 to 47 μg/m^3), probably due to broader regional

25   sources of PM$_{2.5}$, whereas elemental carbon concentrations (EC) showed a four-fold range of site-

26   to-site variations, reflecting the greater local variation in EC from DEP.

27   Several PM health studies for the city of Seattle (King County), WA (e.g. Levy et al., 2001,

28   for out-of-hospital primary cardiac arrests) have found few statistically significant relationships,

29   attributed by the authors in part to the fact that Seattle has a topographically diverse terrain with

30   local "hot spots" of residential wood burning, especially in winter. Sheppard et al. (2001) have

31   explored reasons for these findings, particularly focusing on adjustments for location by use of a

1   "topographic index" that includes the "downstream" normal flow of wood smoke from higher

2   elevations, and the trapping of wood smoke in topographic bowls or basins even at higher

3   elevations. They also adjusted for weather using a "stagnation index" (the average number of

4   hours per day with wind speed less than the 25th percentile of wind speeds), and temperature, as

5   well as interaction terms for stagnation on hilltop sites and temperature at suburban wood-

6   smoke-exposed valley sites. The adjustments for exposure measurement error based on methods

7   developed in (Sheppard and Damian, 2000; Sheppard et al., 2001) had little effect on effect size

8   estimates for the case-crossover study (Levy et al., 2001), but may be useful in other studies

9   where localized effects are believed to be important, particularly for the gaseous co-pollutants.

10   Daniels et al. (2001) evaluated the relative sources of variability or heterogeneity in

11   monitoring PM_{10} in Pittsburgh, PA in 1996. The site is data-rich, having 25 monitors in a

12   rectangle approximately 40 by 80 km. The authors found no isotropic spatial dependence after

13   accounting for other sources of variability, but an indication of heterogeneity in the variability of

14   the small-scale processes over time and space, and heterogeneity in the mean values and

15   covariate effects across sites. Important covariates included temperature, precipitation, wind

16   speed and direction. The authors concluded that significant unmeasured processes might be in

17   operation. These methods should also be useful in evaluating the spatial and temporal variations

18   in gaseous co-pollutants, where small-scale processes are clearly important.

19

8.4.7.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in Multi-Pollutant Models.

22   The discussion in Zeger et al. (2000) may be interpreted as addressing the question of

23   whether the apparent lack of a $PM_{10-2.5}$ effect in models with both fine and coarse particles

24   demonstrates a "false negative" due to the larger measurement error of coarse particle

25   concentrations. However, the more important question may involve the relative attenuation of

26   estimated effects of $PM_{2.5}$ and gaseous co-pollutants, especially those such as CO that are known

27   to be highly correlated with $PM_{2.5}$. Tables 1 and 2 in (Zeger et al., 2000) may be particularly

28   relevant here. The evidence discussed in this chapter supports the hypothesis that PM has

29   adverse health effects, but leaves open the question as to whether the co-pollutants have effects

30   as well when their exposure is measured much less accurately than that of the PM metric. If both

31   the PM metric and the co-pollutant have effects, Table 1 shows that the co-pollutant effect size

32   estimate may be greatly attenuated and the PM effect size estimate much less so, depending on

1   the magnitude of the correlation between the true PM and gaseous pollutant exposures, and the

2   correlation between their measurement errors. One would expect that $PM_{2.5}$, CO, and NO_2 would

3   often have a high positive correlation, and their "exposure measurement errors" would also be

4   positively correlated if PM and the gaseous pollutants were positively correlated due to common

5   activity patterns, weather, and source emissions. Thus, the line with $corr(x_1,x_2) = 0.5$, $var(\delta_1) =$

6   0.5, $var(\delta_2) = 2$, $corr(\delta_1, \delta_2) = 0.7$ seems appropriate. This implies that the estimated effect of

7   the more accurately measured pollutant is 64% of the true value, and that of the less accurately

8   measured pollutant is 14% of the true value. In view of the substantially greater spatial

9   heterogeneity of traffic-generated ambient pollutants such as CO and NO_2, and the relative

10 (though not absolute) regional spatial uniformity of ambient $PM_{2.5}$ in some cities, but not in

11 others, it is likely that effect size estimates in multi-pollutant models are attenuated downward to

12 a much greater extent for the gaseous co-pollutants than for the PM metric in some cities, but not

13 in others. This may explain part of the heterogeneity of findings for multi-pollutant models in

14 different cities discussed in Section 8.4.2.2.3. Low effect size estimates for the gaseous co-

15 pollutants in a multi-pollutant model should be interpreted cautiously, as noted in Section

16 8.4.2.2.3. The representativeness of the monitoring sites for population exposure of both the

17 particle metrics and gaseous pollutants should be evaluated as part of the interpretation of the

18 analysis. Indices such as the maximum 90th percentile of the absolute difference in

19 concentrations between pairs of sites as well as the median cross-correlation across sites may be

20 useful for characterizing for spatially heterogeneity of gaseous co-pollutants as well as for fine

21 particles.

22

23 ## 8.4.7.5 Air Pollution Exposure Proxies in Long-Term Mortality Studies

24   The AHSMOG Study of mortality (Abbey et al., 1999; McDonnell et al., 2000), the

25 Harvard 6-Cities Study of mortality (Dockery et al, 1993), the ACS Study (Pope et al., 1995), and

26 the VA/Washington Univ. Study (Lipfert et al., 2000b) together provided a major step forward in

27 the assessment of the long-term effects of air pollution. These cohort studies responded to many

28 of the major criticisms of the prior cross-sectional mortality studies, while largely confirming the

29 results of those prior studies. In particular, unlike the ecological cross-sectional studies, these

30 new cohort studies had individual-level information about the members of the study cohort,

1   allowing the analysis to more properly control for other major factors in mortality, such as

2   smoking and socio-economic factors.

3   While several of these studies made use of newly available fine particle mass ($PM_{2.5}$) data

4   to derive useful estimates of health effects of $PM_{2.5}$ well before it was routinely measured, these

5   studies utilized air pollution exposure information in a manner similar to that used in the past

6   studies. These studies used central site metropolitan area (MA) spatial and time averages of air

7   pollution exposures, rather than exposure information at the individual level. For this reason, the

8   AHSMOG, Harvard Six-Cities, ACS, and VA/Washington Univ. studies have been term

9   "semi-individual" cohort studies of air pollution.

10

11   **The AHSMOG Study**

12   Although this study covers a large number of years (1977-1992 in Abbey et al., 1999), it is

13   considerably more limited in the availability of particle metrics that were actually observed rather

14   than estimated. Prior to 1987, PM_{10} could only be estimated from TSP, not observed. Likewise,

15   for the more recent years, McDonnell et al. (2000) used participants who lived near an airport so

16   that $PM_{2.5}$, and $PM_{10-2.5}$ as the difference of PM_{10} and $PM_{2.5}$, could be estimated from airport

17   visibility data using the method described in an earlier publication (Abbey et al., 1995b). All of

18   these issues add potential measurement error to the exposure estimates.

19

20   **The Veterans' Administration/Washington University Study**

21   The air pollution concentrations for the participants' counties of residence at the time of

22   enrollment were used in the analyses, rather concentrations at the 32 VA hospitals in the final

23   study. County-wide pollution variables for five particle metrics and three gaseous pollutants

24   were used in the study, although TSP was most often the particle metric observed for the earlier

25   years of the study (before 1975 up to1988), which are important in assessing pollution effects for

26   many years of exposure. However, IPMN data for fine particles and sulfates were available for

27   ca. 1979-1983, as in the ACS study. Effects on average mortality for the intervals 1976-1981,

28   1982-1988, and 1989-1996 were related to multi-year particle exposures for four long intervals:

29   < 1975, 1975-1981, 1982-1988, and 1989-1996. TSP was used in the first three exposure

30   intervals, PM_{10} in the most recent. This study examined "concurrent" exposures (same interval

31   as average mortality), "causal" prior exposures (exposure interval precedes mortality interval),

1   and "non-causal" PM vs. mortality associations. The mortality associations were also examined

2   for $PM_{2.5}$, PM_{15}, and $PM_{15-2.5}$ for 1979-1981 and 1982-1984. This study has a considerable

3   amount of air pollution data and should be as adequate as other studies for characterizing fixed-

4   site air pollution concentrations in the place of residence at the time of enrollment. However, if

5   any participants moved away from the county where air pollution is measured, but were retained

6   in the study because they continue to participate in follow-ups at the same clinic, then the use of

7   the initial residence location may not be an adequate proxy for actual exposure after initial

8   enrollment.

9

10   **Harvard Six-Cities Air Pollution Exposure Data**

11   In the case of the Harvard Six Cities Study, ambient concentrations of fine particles ($PM_{2.5}$),

12   total suspended particles (TSP), sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), and

13   sulfate ($SO_4^=$) were measured at a centrally located air monitoring station established within each

14   of the six communities. Long-term mean concentrations for each pollutant were calculated for

15   periods that were consistent among the six cities, but not across pollutants. The original

16   epidemiologic analysis characterized ambient air quality as long-term mean concentrations of

17   total particles (TSP) (1977-1985), inhalable and fine particles (1979-1985), sulfate particles

18   (1979-1984), aerosol acidity (H^+) (1985–1988), sulfur dioxide (1977-1985), nitrogen dioxide

19   (1977-1985), and ozone (1977-1985), as follows:

20   Gases: The gases (SO_2, NO_2, and O_3) were monitored hourly by conventional continuous

21   instrumentation in parts per billion.

22

23   Particles: Mean PM concentrations were reported for four classifications of particles in each of

24   the six cities: TSP (particles with aerodynamic diameters up to 50 μm), inhalable particles, fine

25   particles, and sulfate particles. Values of mass for TSP and sulfate particles were determined

26   from 24-h high-volume samplers. Inhalable particle mass was calculated from coarse and fine

27   particle mass, which had been determined from 24-h sample pairs collected by dichotomous

28   samplers. In these, the fine particle channel collected particles smaller than about 2.5 μm and the

29   measurement was recorded directly as fine particle (FP) mass. The coarse particle channel

30   collected particles between 2.5 μm and 10 or 15 μm in aerodynamic diameter (the upper bound

31   measurement depended on the inlet size used at the time).

1   <u>Acidity</u>: Aerosol acidity (H$^+$) was measured for about one year in each city. However,

2   measurements were conducted in only two cities at a time. Thus, it was not possible to compare

3   acidity for a common time period. Furthermore, the acidity data were not linked with particle

4   data in the same city. Thus, intercity and inter-pollutant comparisons of H$^+$ in this study were

5   confounded by inter-annual variability.

6

7   **ACS Study Air Pollution Exposure Data**

8   In the ACS Study (Pope et al., 1995), two measures of particulate air pollution, were

9   considered: fine particles and sulfate. No gaseous pollutants were considered. The mean

10   concentration of sulfate air pollution by metropolitan area (MA) during 1980 was estimated using

11   data from the EPA Aerometric Information Retrieval System (AIRS) database. These means

12   were calculated as the averages of annual arithmetic mean 24-h sulfate values for all monitoring

13   sites in the 151 MA's considered. The median concentration of fine particles between 1979 and

14   1983 was estimated from the EPA's dichotomous sampler network. These estimates of fine

15   particle levels had been used previously in a population-based cross-sectional mortality study of

16   50 MA's. Gaseous co-pollutants were not considered in Pope et al's original ACS analysis.

17

18   **Six-City Study and ACS Exposure Data Strengths and Weaknesses**

19   In each of these studies, there was a single mean pollution concentration assigned for each

20   city for each pollutant for the entire follow-up period considered. Concentrations were not

21   broken into each year or sub-groups of years (e.g., 5 year averages), largely because data were not

22   available in this form. This may represent a significant weakness, as a single number could not

23   accurately account for the different exposures in different years of follow-up. However, it is

24   possible that the simultaneous or immediately preceding years alone might not as well represent

25   the effects of long-term pollution exposure.

26   The ACS analysis also uses metropolitan area (MA) pollutant concentrations for air

27   pollution exposure estimates, rather than individual level measurements. Thus, spatial variability

28   in air pollution levels and potential effects of different housing infiltration rates were not

29   addressed as potential factors in exposure variability. However, individual exposure data would

30   be economically impractical for such large cohorts, and the use of more localized measurements

31   (e.g., by county) might well lead to more error, due to day-to day mobility between counties by

1   individuals (e.g., to work and back) and changes of specific residence within an MA over time.

2   Thus, the MA average may yet be the best metric that can be developed in the absence of

3   individual level exposure data.

4   Another notable weakness of the original ACS Study was that only two PM air pollution

5   metrics were considered. Thus, this study did not consider the potentially confounding

6   influences of gaseous air pollutants or other particle indicators.

7   These two studies' analyses assign the subjects' residence MA on the basis of where they

8   were enrolled, which can lead to exposure errors if the subjects moved to another MA during the

9   follow-up period. However, a recent reanalysis of the Six Cities Study cohort (Krewski et al.,

10   2000) indicates that mobility in these older populations is limited, with only 18.5% leaving the

11   original city of enrollment over subsequent decades.

12

13   **The HEI Reanalysis of the ACS Study**

14   The HEI Reanalysis of these two cohort studies (Krewski et al, 2000) confirmed the

15   databases used in these two studies, but also developed new exposure data for the ACS Study

16   cohort. In particular, data for the gaseous pollutants (for the year 1980) were added to the

17   analysis. Table 8-43 below displays summary data for the most recent data available for the

18   analysis of the ACS cohort (Pope et al., 2002). The variables noted with the data source "HEI"

19   were added to the analysis during the HEI reanalysis. These HEI results largely confirmed the

20   original ACS analysis results for PM, but also indicated that SO_2 was also correlated with U.S.

21   mortality.

22

23   **The 16-Year Follow-Up of the ACS Cohort**

24   Also included in Table 8-43 are summaries of the pollutant data developed to provide

25   exposure estimates for the latest 16-year follow-up analysis of the ACS cohort (Pope et al, 2002).

26   These new data are similarly city-wide averages of all monitoring stations in the MA's

27   considered, but for the entire period of follow-up (1982-1998), when possible. In addition, this

28   new analysis has incorporated the new $PM_{2.5}$ air monitoring data collected routinely from 1999

29   onward. As a result, this new analysis has increased the analysis power both by extending the

30   length of follow-up, and by adding significant new multiple and multi-year air pollution exposure

31   data to the analysis.

**TABLE 8-43. SUMMARY OF ACS POLLUTION INDICES: UNITS, PRIMARY
SOURCES, NUMBER OF CITIES AND SUBJECTS AVAILABLE FOR ANALYSIS,
AND THE MEAN LEVELS (standard deviations)**

Pollutant (years of data)	Units	Sources of Data[*]	No. of Metro Areas	No. of Sub. (1000s)	Mean (SD)
$PM_{2.5}$ (79-83)	$\mu g/m^3$	IPMN (HEI)	61	359	21.1 (4.6)
$PM_{2.5}$ (99-00)	$\mu g/m^3$	AIRS (NYU)	116	500	14.0 (3.0)
$PM_{2.5}$ (ave)	$\mu g/m^3$	Average of two above	51	319	17.7 (3.7)
PM_{10} (82-98)	$\mu g/m^3$	AIRS (NYU)	102	415	28.8 (5.9)
PM_{15} (79-83)	$\mu g/m^3$	IPMN (HEI)	63	359	40.3 (7.7)
$PM_{15-2.5}$ (79-83)	$\mu g/m^3$	IPMN (HEI)	63	359	19.2 (6.1)
TSP (80-81)	$\mu g/m^3$	NAD (HEI.)	156	590	68.0 (16.7)
TSP (79-83)	$\mu g/m^3$	IPMN (HEI)	58	351	73.7 (14.3)
TSP (82-98)	$\mu g/m^3$	AIRS (NYU)	150	573	56.7 (13.1)
SO_4 (80-81)	$\mu g/m^3$	IPMN and NAD, artifact adjusted (HEI)	149	572	6.5 (2.8)
SO_4 (90)	$\mu g/m^3$	NYU compilation and analysis of PM_{10} filters	53	269	6.2 (2.0)
SO_2 (80)	ppb	AIRS (HEI)	118	520	9.7 (4.9)
SO_2 (82-98)	ppb	AIRS (NYU)	126	539	6.7 (3.0)
NO_2 (80)	ppb	AIRS (HEI)	78	409	27.9 (9.2)
NO_2 (82-98)	ppb	AIRS (NYU)	101	493	21.4 (7.1)
CO (80)	ppm	AIRS (HEI)	113	519	1.7 (0.7)
CO (82-98)	ppm	AIRS (NYU)	122	536	1.1 (0.4)
O_3 (80)	ppb	AIRS (HEI)	134	569	47.9 (11.0)
O_3 (82-98)	ppb	AIRS (NYU)	119	525	45.5 (7.3)
O_3 (82-98 3rd Q.)	ppb	AIRS (NYU)	134	557	59.7 (12.8)

Source: Pope et al. (2002)

Conclusions

The pollution exposure data used in these studies, while state-of-the-art when they were
conducted, have weaknesses, most notably that these studies, of necessity, have employed city-
wide estimates of air pollution exposure, rather than individual-level exposure data. In the case
of the mortality control variables (e.g., race and education), the use of individual-level data did

1 not significantly change the air pollution effect estimates from those given by prior "ecological"

2 cross-sectional mortality analyses using MA aggregate data (e.g., Ozkaynak and Thurston, 1987).

3 Future research into the human health effects of long-term air pollution exposures needs to

4 similarly assess whether the use of individual level exposure data would or would not

5 substantially change the pollution effect estimates.

6

8.4.9 Heterogeneity of Particulate Matter Effects Estimates

8   Approximately 35 then-available acute PM exposure community epidemiologic studies

9 were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality

10 being associated with short-term (24-h) PM exposures indexed by various ambient PM

11 measurement indices (e.g., PM_{10}, $PM_{2.5}$, BS, COH, sulfates, etc.) in many different cities in the

12 United States and internationally. Much homogeneity appeared to exist across various

13 geographic locations, with many studies suggesting, for example, increased relative risk (RR)

14 estimates for total nonaccidental mortality on the order of 1.025 to 1.05 (or 2.5 to 5.0% excess

15 deaths) per 50 $\mu g/m^3$ increase in 24-h PM_{10}, with statistically significant results extending more

16 broadly in the range of 1.5 to 8.0%. The elderly $\geq$ 65 yrs. old and those with preexisting

17 cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City

18 Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to

19 1.056 (2.0 to 5.6% excess deaths) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.

20   Now, more than 80 new time-series PM-mortality studies assessed earlier in this chapter

21 provide extensive additional evidence which, qualitatively, largely substantiates significant

22 ambient PM-mortality relationships, again based on 24-h exposures indexed by a wide variety of

23 PM metrics in many different cities of the United States, in Canada, in Mexico, and elsewhere (in

24 South America, Europe, Asia, etc.). The newly available effect size estimates from such studies

25 are reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996

26 PM AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0%

27 excess deaths per 50 $\mu g/m^3$ PM_{10} increment in 24-h concentration; whereas new $PM_{2.5}$ excess

28 estimates for short-term exposures generally fall in the range of 2 to 8% per 25 $\mu g/m^3$ increment

29 in 24-h $PM_{2.5}$ concentration.

30   However, somewhat greater spatial heterogeneity appears to exist across newly reported

31 study results, both with regard to PM-mortality and morbidity effects. The newly apparent

1   heterogeneity of findings across locations is perhaps most notable in relation to reports based on

2   multiple-city studies in which investigators used the same analytical strategies and models

3   adjusted for the same or similar co-pollutants and meteorological conditions, raising the

4   possibility of different findings reflecting real location-specific differences in exposure-response

5   relationships rather than potential differences in models used, pollutants measured and included

6   in the models, etc. Some examples of newly reported and well-conducted multiple-city studies

7   include: the NMMAPS analyses of mortality and morbidity in 20 and 90 U.S. cities (Samet et al.,

8   2000a,b; Dominici et al., 2000a); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of

9   eight largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S.

10   counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several

11   European cities (Katsouyanni et al., 1997; Zmirou et al., 1998). The recently completed large

12   NMMAPS studies of morbidity and mortality in U.S. cities add especially useful and important

13   information about potential U.S. within- and between-region heterogeneity.

14

15   **8.4.9.1 Evaluation of Heterogeneity of Particulate Matter Mortality Effect Estimates**

16   In all of the U.S. multi-city analyses, the heterogeneity in the PM estimates across cities

17   was not explained by city-specific characteristics in the 2nd stage model. The heterogeneity of

18   effects estimates across cities in the multi-city analyses may be due to chance alone, to mis-

19   specification of covariate effects in small cities, or to real differences from location to location in

20   effects of different location-specific ambient PM mixes, for which no mechanistic explanations

21   are yet known. Or, the apparent heterogeneity may simply reflect imprecise PM effect estimates

22   derived from smaller-sized analyses of less extensive available air pollution data or numbers of

23   deaths in some cities tending to obscure more precise effects estimates from larger-size analyses

24   for other locations, which tend to be consistently more positive and statistically significant.

25   Some of these possibilities can be evaluated by using data from the NMMAPS study

26   (Samet et al., 2000b). Data in Figure 8-3 were optically scanned and digitized, producing

27   reasonably accurate estimates by comparison with the 20 largest U.S. cities in their Table A-2.

28   The cities were divided among 7 regions, and excess risk with 95% confidence intervals plotted

29   against the total number of effective observations, measured by the number of days of PM_{10} data

30   times the mean number of daily deaths in the community. This provides a useful measure of the

31   weight that might be assigned to the results, since the uncertainty of the RR estimate based on a

1   Poisson mean is roughly inversely proportional to this product. That is, the expected pattern

2   typically shows less spread of estimated excess risk with increasing death-days of data. A more

3   refined weight index would also include the spread in the distribution of PM concentrations. The

4   results are plotted in Figure 8-30 for all cities and Figure 8-31 for each of the 7 regions.

5   Figure 8-30 for all cities suggests some relationship between precision of the effects

6   estimates and study weight, overall. That is, the more the mortality-days observations, the

7   narrower the 95% confidence intervals and the more precise the effects estimates (with nearly all

8   these for cities with $\geq$ log 9 mortality-days being positive and many statistically significant at

9    $p \leq 0.05$).

10   The Figure 8-31 depiction for each of the 7 regions is also informative. In the Northeast,

11   there is considerable homogeneity (not heterogeneity) of effect size for larger study-size cities,

12   even with moderately wide confidence intervals for those with log mortality-days = 8 to 9, and all

13   clearly exceed the overall nationwide grand mean indicated by the dashed line. On the other

14   hand, the smaller study-size Northeast cities (with much wider confidence intervals at log

15   < 8) show much greater heterogeneity of effects estimates and less precision. Also, most of the

16   estimates for larger study-size (log > 9) cities in the industrial midwest are positive and several

17   statistically significant, so that an overall significant regional risk is plausible there as well. There

18   may even be some tendency for relatively large risks for some cities with small study sizes and

19   wide confidence intervals in the industrial midwest, and further investigation of that would be of

20   interest. The plot for Southern California in Figure 8-31 clearly shows a rather consistent

21   estimate of effect size and width of the confidence intervals across cities of varying study-size.

22   All risk estimates are positive and most are significant at $p \leq 0.05$ or nearly so for the Southern

23   California cities. For Northwestern cities plotted in Figure 8-31, the value for Oakland, CA (at

24   ca. log 9.5) is notable (it being very positive and significant), whereas many but not all of the

25   other cities have positive effect estimates not too far off the nationwide grand mean, but with

26   sufficiently wide confidence intervals so as not to be statistically significant at $p \leq 0.05$. The

27   Southwestern cities (except for 2 cities), too, mostly appear to have effect sizes near the

28   nationwide mean, but with confidence intervals too wide to be significant at $p \leq 0.05$. The

29   "Other" (non-industrial or "Upper", as per NMMAPS) Midwest cities and the Southeastern cities

30   in Figure 8-31 show more heterogeneity, although most of the larger study size cities (log ≥ 9.0)

31   tend to be positive and not far off the nationwide mean (even though not significant at $p \leq 0.05$).
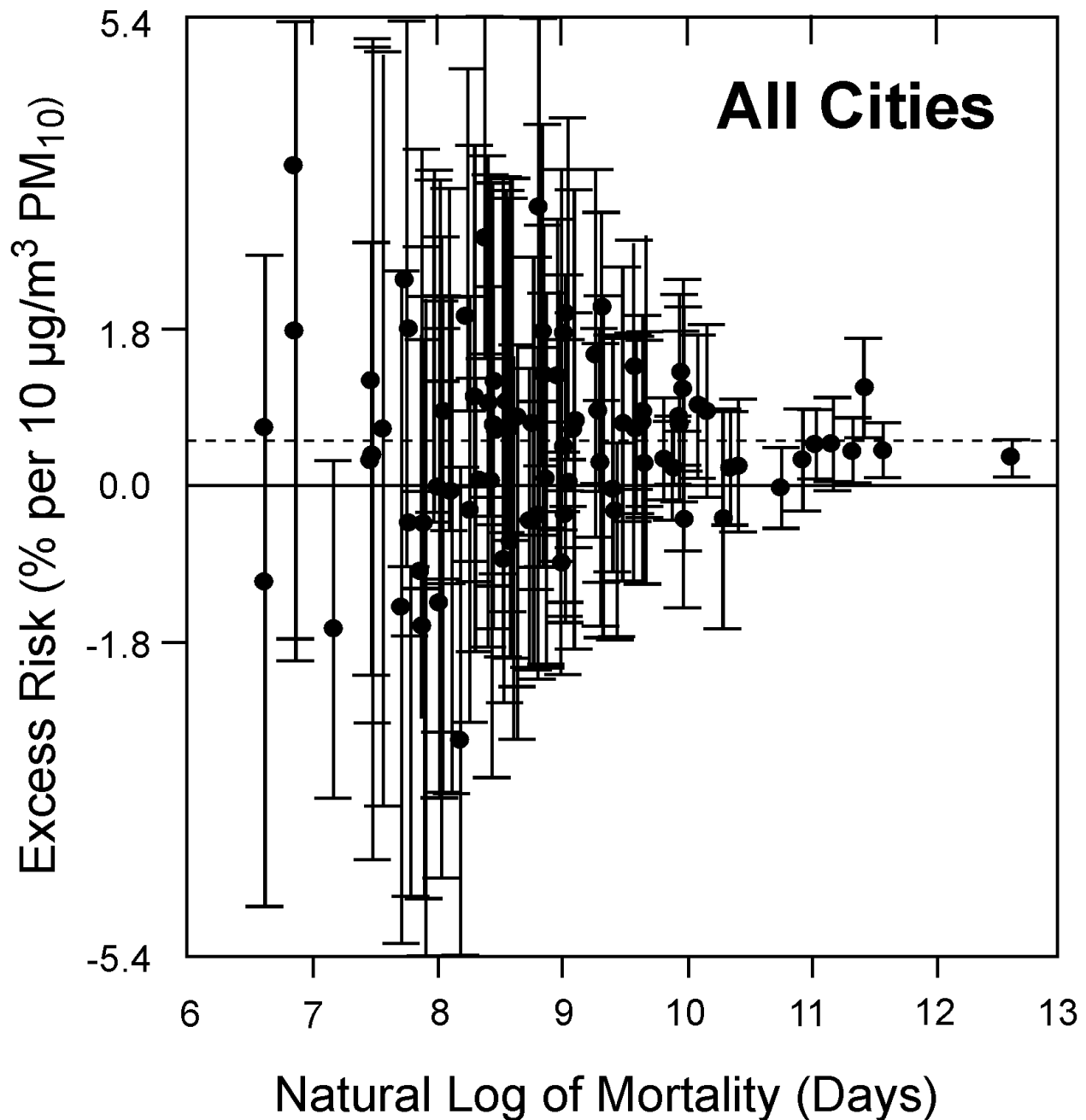
Figure 8-30. The EPA-derived plot showing relationship of PM_{10} total mortality effects estimates and 95% confidence intervals for all cities in the Samet et al. (2000a,b) NMMAPS 90-cities analyses in relation to study size (i.e., the natural logarithm or numbers of deaths times days of PM observations). Note generally narrower confidence intervals for more homogeneously positive effects estimates as study size increases beyond about ln (mortality-days) (i.e., beyond about 8,000 deaths-days of observation). The dashed line depicts the overall nationwide effect estimate (grand mean) of approximately 0.5% per 10 $\mu g/m^3$ PM_{10} for models with no co-pollutants.
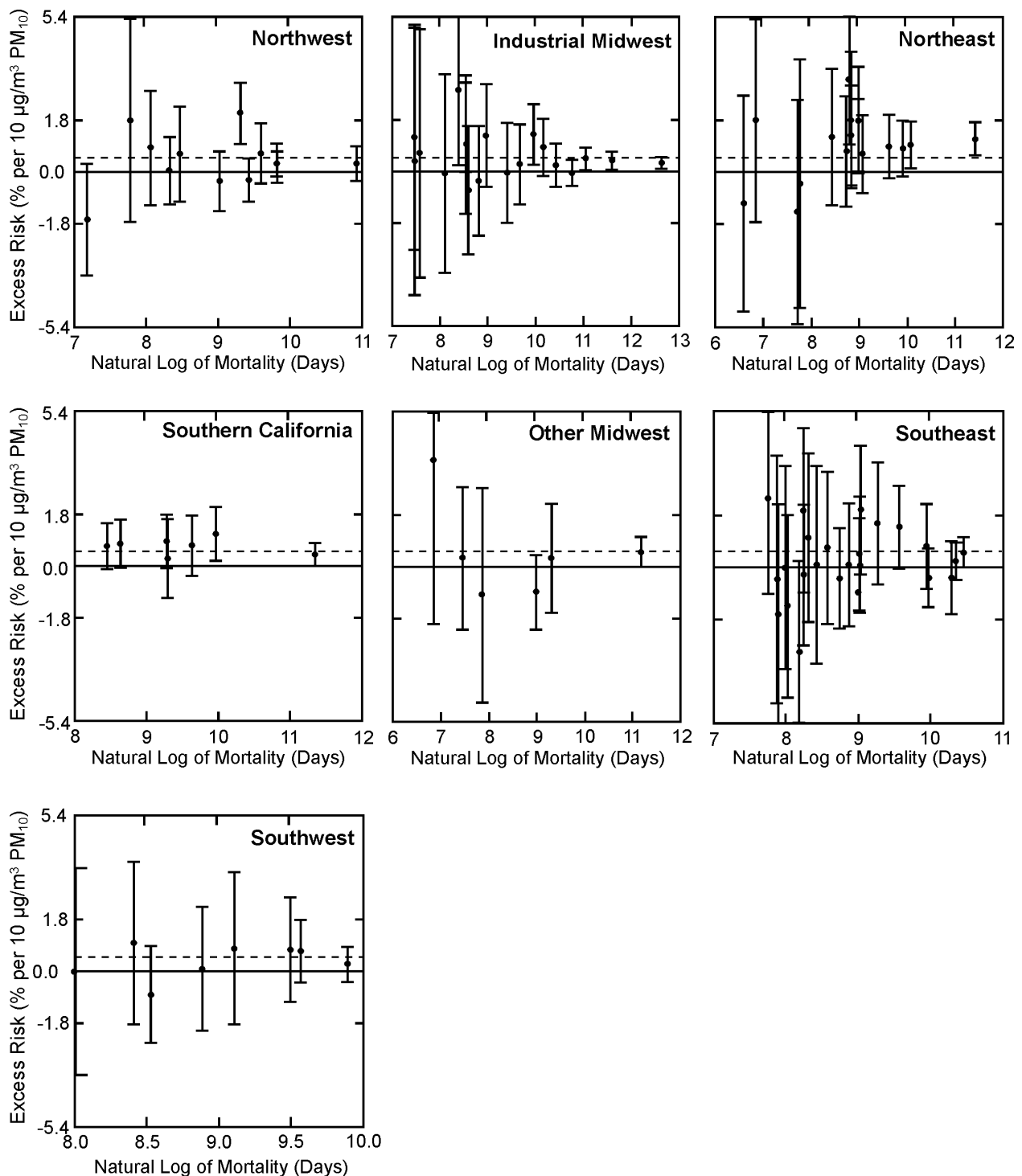
Figure 8-31. The EPA-derived plots showing relationships of PM$_{10}$-mortality (total, nonaccidental) effects estimates and 95% confidence intervals to study size (defined as Figure 8-10) for cities broken out by regions as per the NMMAPS regional analyses of Samet et al. (2000a,b). Dashed line on each plate depicts overall nationwide effect estimate (grand mean) of approximately 0.5% per 10 μg/m^3 PM$_{10}$ for models with no co-pollutants.

1   Given the wide range of effects estimates and confidence intervals seen for Southeastern cities,

2   further splitting of the region might be informative.

3   In fact, closer reexamination of results for each of the regions may reveal interesting new

4   insights into what factors may account for any apparent disparities among the cities within a

5   given region or across regions. Several possibilities readily come to mind. First, cursory

6   inspection of the mean PM_{10} levels shown for each city in (Samet et al., 2000b; Appendix A)

7   suggests that many of the cities showing low effects estimates and wide confidence intervals tend

8   to be among those having the lowest mean PM_{10} levels and, therefore, likely the smallest range of

9   PM_{10} values across which to distinguish any PM-related effect, if present. It may also be possible

10   that those areas with higher $PM_{2.5}$ proportions of PM_{10} mass (i.e., larger percentages of fine

11   particles) may show higher effects estimates (e.g., in Northeastern cities) than those with higher

12   coarse-mode fractions (e.g., as would be more typical of Southwestern cities). Also, more

13   industrialized cities with greater fine-particle emissions from coal combustion (e.g., in the

14   industrial Midwest) and/or those with high fine-particle emissions from heavy motor vehicle

15   emissions (e.g., typical of Southern California cities) may show larger PM_{10} effects estimates

16   than other cities. Lastly, the extent of air-conditioning use may also account for some of the

17   differences, with greater use in many Southeastern and Southwestern cities perhaps decreasing

18   actual human exposure to ambient particles present versus higher personal exposure to ambient

19   PM (including indoors) in those areas where less air-conditioning is used (e.g., the Northeast and

20   industrial Midwest). See, for example, Janssen et al. (2002) results reproduced as Figure 8-11.

21

22   **8.4.9.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses**
23   **Studies**

24   Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of

25   U.S. cities to allow considerable resolution of regional PM effects within the "lower 48" states,

26   but an attempt was made to take this approach to a much more detailed level in the Cohort

27   Reanalysis studies than in NMMAPS. There were: 88 cities with PM_{10} effect size estimates in

28   NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in the original Pope et al. (1995)

29   ACS analyses and in the HEI reanalyses using the original data; and 63 cities with $PM_{2.5}$ data and

30   144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis team.

31   The relatively large number of data points utilized in the HEL reanalyses effort and additional

1   analyses allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates,

2   and SO_2 with resolution on a scale of a few tens to hundreds of kilometers.

3   The patterns for $PM_{2.5}$ and sulfates are similar, but not identical. In particular, the modeled

4    $PM_{2.5}$ surface (Krewski et al., 2000; Figure 18) has peak levels around Chicago - Gary, in the

5   eastern Kentucky - Cleveland region, and around Birmingham AL, with elevated but lower $PM_{2.5}$

6   almost everywhere east of the Mississippi, as well as southern California. This is similar to the

7   modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in

8   Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated SO_2

9   concentrations is the Cleveland - Pittsburgh region. A preliminary evaluation is that secondary

10   sulfates in particles derived from local SO_2 are more likely to be important in the industrial

11   midwest, south from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia,

12   and southwest Pennsylvania, possibly related to combustion of high-sulfur fuels.

13   The overlay of mortality with air pollution patterns is also of much interest. The spatial

14   overlay of long-term $PM_{2.5}$ and mortality (Krewski et al., 2000; Figure 21) is highest from

15   southern Ohio to northeastern Kentucky/West Virginia, but also includes a significant association

16   over most of the industrial midwest from Illinois to the eastern non-coastal parts of North

17   Carolina, Virginia, Pennsylvania, and New York. This is reflected, in diminished form, by the

18   sulfates and SO_2 maps (Krewski et al., 2000; Figures 19 and 20), where there appears to be a

19   somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that,

20   while SO_2 may be an important precursor of sulfates in this region, there may also be some other

21   (non-sulfur) contributors to associations between $PM_{2.5}$ and long-term mortality, embracing a

22   wide area of the North Central Midwest and non-coastal Mid-Atlantic region.

23   It should be noticed that, while a variety of spatial modeling approaches were discussed in

24   the NMMAPS methodology report (NMMAPS Part I, pp. 66-71 [Samet et al., 2000a]), the

25   primary spatial analyses in the 90-city study (NMMAPS, Part II [Samet et al., 2000b]) were

26   based on a simpler seven-region breakdown of the contiguous 48 states. The 20-city results

27   reported for the spatial model in NMMAPS I show a much smaller posterior probability of a

28   PM_{10} excess risk of short-term mortality, with a spatial posterior probability vs. a non-spatial

29   probability of a PM_{10} effect of 0.89 vs. 0.98 at lag 0, of 0.92 vs. 0.99 at lag 1, and of 0.85 vs. 0.97

30   at lag 2. The evidence that PM_{10} is associated with an excess short-term mortality risk is still

31   moderately strong with a spatial model, but less strong than with a non-spatial model.

1   The apparently substantial differences in PM_{10} and/or $PM_{2.5}$ effect sizes across different

2   regions should not be attributed merely to possible variations in measurement error or other

3   statistical artifact(s). Some of these differences may reflect: real regional differences in particle

4   composition or co-pollutant mix; differences in relative human exposures to ambient particles or

5   other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in

6   regional population); or other important, as of yet unidentified PM effect modifiers.

7

8   **8.4.9.3 Epidemiologic Studies of Ambient Air Pollution Interventions**

9   To date, assessment of health risk in epidemiologic studies of ambient air pollutants,

10   including PM, has relied largely on studies that focus on increases in exposure, and that inquire

11   whether health risk changes in relation to such increases. Such studies are used to support

12   qualitative and quantitative inference as to whether decreases in exposure will bring about

13   reductions in health risk, or improvement in health status.

14   Ambient criteria air pollutants are rarely, if ever, the only etiology of the health disorders

15   with which exposure to these pollutants is associated. For example, numerous reports have

16   implicated ambient air pollution exposure with exacerbations of pre-existing asthma. These

17   reports justify the expectation that further reduction in ambient air pollution exposure would

18   reduce the public health burden of asthma exacerbations. However, many other factors,

19   including allergens, passive smoking, exercise, cold, and stress are also associated with such

20   exacerbations. Asthmatics would continue to be exposed to these factors even with further

21   reduction in ambient air pollution exposure.

22   Thus, reduction of ambient air pollution exposure, even to zero concentration, would not

23   bring about zero risk of the health disorders with which such exposure is associated. Also, it is

24   likely that at least some non-pollution risk factors would behave differently in the absence of

25   ambient air pollution exposure as in its presence. That is, in the real world, risk factors probably

26   do not behave in discrete, additive fashion.

27   Therefore, truly quantitative characterization of effects of reduction in air pollution

28   concentrations and exposures requires study of situations in which such reductions actually

29   occur. In such studies, it is important to measure both exposure and health status before and after

30   exposure is reduced. It is also highly desirable to identify risk factors other than ambient air

31   pollution, and to ascertain their effects before and after air pollution exposure reduction.

1   In his classic monograph (The Environment and Disease: Association or Causation?), Hill

2   (1965) addressed the topic of preventive action and its consequences under Aspect 8, stating:

3   "Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental,

4   evidence. For example, because of an observed association some preventive action is taken. Does

5   it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop

6   smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support

7   for the causation hypothesis may be revealed."

8   The available epidemiologic literature on ambient air pollution offers a limited evidence

9   related to this aspect. In these studies, air pollution concentrations have been temporarily or

10   permanently reduced through regulatory action, industrial shutdown, or other intervening

11   factor(s).

12   In the U.S., the most thoroughly studied example of such ambient air pollution reduction

13   occurred in the Utah Valley, UT, during the 1980s. The Valley's largest stationary source of PM,

14   a steel mill, was closed due a labor dispute for 13 months from autumn 1986 until autumn 1987.

15   This offered the opportunity to study health effects not only of the closure-related reduction in

16   ambient PM concentrations, but also of the increases in PM that occurred after the re-opening of

17   the mill. Pope et al. have reported extensively on such health effects. These reports were

18   addressed in more detail in the 1996 PM AQCD than in the present document. Briefly, these

19   investigators observed reduction in frequency of a variety of health disorders during the period in

20   which the mill was closed. These included daily mortality (Pope et al., 1992), respiratory

21   hospital admissions (Pope, 1989), bronchitis and asthma admissions for preschool children

22   (Pope, 1991), reductions in lung function (Pope et al., 1991), and elementary school absences

23   (Ransom and Pope, 1992). Changes in these endpoints were reflected by differing strength of

24   positive associations between measures of these health endpoints and PM mass measurements

25   from filters collected before, during, and after the steel mill shut down.

26   Five experimental studies investigated effects of aqueous extracts of ambient Utah Valley

27   particulate filters employing filter extracts from January through March 1986 (mill open), 1987

28   (mill closed), and 1988 (mill open) (Frampton et al., 1999; Dye et al., 2001; Soukup et al., 2000;

29   Wu et al., 2001; and Ghio and Devlin, 2001). In all of these studies, investigators observed less

30   intense in vivo or in vitro effects when treating with the 1987 extracts than when treating with

31   extracts from 1986 and/or 1987 (see Chapter 7 of this document).

1   Frampton et al. (1999) state that extracts were taken from filters collecting PM_{10}, and that a

2   total of 36 filters was used, 12 per year. Soukup et al. (2000) state that PM_{10} filters were used,

3   and that 34 filters per year were used (total 102 filters). Dye et al. (2001) state that TSP filters

4   were extracted, and that 12 filters per year were used (total 36 filters). Wu et al. (2001) state that

5   PM_{10} filters were used, and a total of 102 filters was used. Ghio and Devlin (2001) state that

6   "filters containing PM_{10}" were extracted, and that 34 filters each year were used (total 102

7   filters). Taken together, these descriptions raise the question whether the two studies that

8   employed 12 filters per year (Frampton et al. and Dye et al.) were using TSP filters exclusively,

9   whereas the other three studies, that employed 34 filters per year, employed a mixture of TSP

10   filters and PM_{10} filters. In any event, the degree of comparability of source filters among these

11   five studies is not entirely clear. Also, there is some uncertainty as to the within-study

12   comparability of filters from year to year, particularly in the studies that employed 34 filters per

13   year. Furthermore, a substantial proportion of the extracted material was probably derived from

14   filter matrix, not ambient PM, and about 10 years elapsed between collection and extraction of

15   the filter samples.

16   Even so, the combined results of these five experimental studies provide support and

17   corroboration for the epidemiologic observations of reduced frequency and severity of health

18   disorders during the period of steel mill closure. The experimental studies also provide

19   hypotheses regarding potential biological mechanisms underlying some of the observed effects.

20   Perhaps the strongest of these hypotheses is that PM-associated metals were etiologically related

21   to some of the observed disorders, and that reduction in ambient concentrations of these metals

22   was at least partially responsible for the health benefits observed during steel mill closure. In any

23   event, these experimental studies underscore the importance of particle composition in

24   production or promotion of harmful health effects (Beckett, 2001).

25   Avol and colleagues investigated effects of reductions and increases in ambient air

26   pollution concentrations on longitudinal lung function growth in a subsample of participants in

27   the Children's Health Study conducted by the University of Southern California (Avol et al.,

28   2001). Follow-up lung function tests were administered to 110 children who had moved away

29   from the study area after the baseline lung function test, which was administered while the

30   children lived within the study area. Lung function growth rates were analyzed against

31   differences between the children's original and new communities in annual average

1 concentrations of PM_{10}, NO_2, and O_3. Analytical models were adjusted for anthropometric

2 variables and other relevant covariates. No multi-pollutant analyses were reported. Moving to a

3 community with lower ambient PM_{10} concentration was associated with increased growth rates of

4 FVC, FEV1, MMEF and PEFR, and moving to a community with higher PM_{10} concentrations

5 was associated with decreased growth of these metrics. These associations were statistically

6 significant for MMEF and PEFR, and appear to have been marginally significant for FVC and

7 FEV1. Moving to a community with lower ambient NO_2 or O_3 concentration was generally

8 associated with increased lung function growth, and vice versa. However, associations of change

9 in lung function growth with change in community levels of NO_2 and O_3 were not statistically

10 significant. This study suggests that reduction in long-term ambient PM_{10} levels is indeed

11 associated with improvement of children's lung growth, and that increase in these levels is

12 associated with retardation of lung growth.

13   Friedman et al. (2001) investigated the influence of temporary changes in transportation

14 behaviors (instituted to reduce downtown traffic congestion during the 1996 Summer Olympic

15 Games in Atlanta, GA) on ambient air quality and acute care visits and hospitalizations for

16 asthma in children residing in Atlanta. Ambient air quality and childhood asthma during the

17 17 days of the Games were compared to those during a baseline period consisting of the four

18 weeks before and the four weeks after the Games. During the Games, concentrations of PM_{10}

19 (24-h average), O_3 (daily peak 1-h average), CO (8-h average), and NO_2 (daily peak 1-h average)

20 were, respectively, 16.1%, 27.9%, 18.5%, and 6.8% lower than during the baseline period.

21 Twenty-four hour average concentrations of SO_2 were 22.1% higher during the Games than

22 during the baseline period. Reductions in O_3, PM_{10}, and carbon monoxide were statistically

23 significant at alpha = 0.05 (p = 0.01, p < 0.001, and p = 0.02, respectively). Ambient mold

24 counts during the Games did not differ significantly from those during the baseline period. Four

25 sources of asthma frequency data were examined: (1) the Georgia Medicaid claims file; (2) files

26 of a health maintenance organization; (3) emergency department records for two of Atlanta's

27 three pediatric hospitals; and (4) the Georgia Hospital Discharge Database. For all four sources,

28 asthma-related unadjusted and adjusted relative risks during the Games were less than 1 (as

29 compared to RR = 1 during the baseline period). Relative risks from the Medicaid database were

30 statistically significant (p $\leq$ 0.005), and those from the HMO approached significance (p $\leq$ 0.10).

31 These findings suggest strongly that, in Atlanta in summer 1996, temporary improvement in

1   ambient air quality contributed to temporary reduction in severity of pre-existing asthma. This

2   reduction could not be attributed specifically to any individual air pollutant. In the opinion of

3   Friedman et al., reductions in morning rush-hour traffic played an important role in reduction of

4   asthma-related visits and hospitalizations.

5   Heinrich et al. (2000) studied effects of long-term air pollution reduction in the former East

6   Germany on prevalence of respiratory illnesses and symptoms in 5 to 14 year-old children.

7   Cross-sectional surveys were conducted in 1992-1993 and 1995-1996 in three areas, all of which

8   experienced reductions in annual mean ambient SO_2 and TSP concentrations in the time interval

9   between the surveys. Percentage reductions in SO_2 and TSP were substantial, ranging from

10 about 40%-60% and about 20%-35%, respectively, in the three areas. Longitudinal changes were

11 not measured for size-specific PM metrics. After adjustment for relevant covariates, statistically

12 significant temporal decreases in prevalences of bronchitis, otitis media, frequent colds, and

13 febrile infections were observed.

14   In Hong Kong, a regulation prohibiting the use of fuel oil containing more than 0.5% sulfur

15 by weight went into effect in July 1990. Investigators from the University of Hong Kong studied

16 respiratory health in children and non-smoking women before and after the regulation was

17 implemented. In a relatively polluted district (District A), the regulation resulted in rapid and

18 substantial reduction in the ambient concentration of sulfur dioxide, and in appreciable but less

19 marked reduction in the concentration of sulfate ion in "respirable suspended particulates" (RSP,

20 thought to be equivalent to PM_{10}). Percentage reductions in these sulfur-containing pollutants

21 were considerably smaller in a less polluted district (District B). The regulation was not

22 accompanied by appreciable reductions in levels of PM metrics (TSP and RSP) in either district.

23   Tam et al. (1994) reported that the prevalence of bronchial hyperreactivity (BHR) in

24 children (as defined by a $\geq$ 20% drop in FEV1 in response to histamine challenge) was higher in

25 District A than in District B, even after exclusion of children with wheeze and asthma. Wong

26 et al. (1998) measured BHR prevalence rates in these districts in 1991 and 1992, and compared

27 these to rates before the regulation was implemented. In both districts, BHR prevalence was

28 statistically significantly lower in 1991 than before the intervention. In 1992, the pre- to post-

29 intervention decrease in BHR prevalence was significantly larger in District A than in

30 District B. Peters et al. reported that before the intervention, prevalences of children's respiratory

31 symptoms (e.g., cough, sore throat, wheeze) were statistically significantly higher in District A

1 than in District B. About one year after the intervention, there were greater pre- to post-

2 intervention declines in prevalences of cough or sore throat, phlegm, and wheezing in District A

3 than in District B. Wong et al. reported that before the intervention, the prevalence of poor

4 respiratory health in non-smoking women was significantly higher in District A than in District

5 B. Also, effects of passive smoking on the women's respiratory health were stronger in District

6 A than in District B, but not significantly so. About one year after the intervention, declines in

7 frequency of poor respiratory health were observed, but these declines did not differ significantly

8 between districts. Taken together, these Hong Kong studies suggest that reduction of sulfur in

9 fuel oil brought about appreciable improvement in children's respiratory health, and discernible

10 but lesser improvement in non-smoking women's respiratory health. These studies also suggest

11 that these benefits were associated with reduction in sulfur-containing ambient air pollutants, but

12 not necessarily with reduction in TSP or RSP per se.

13   Taken together, these epidemiologic intervention studies lend confidence that further

14 reduction of ambient air pollution exposures in the U.S. would benefit public health. It is likely

15 that such reduction would bring about both respiratory and cardiovascular health benefits.

16 Available studies also give reason to expect that further reductions in both particulate and

17 gaseous air pollutants would benefit health. On balance, these studies suggest that selective

18 reduction in ambient PM concentrations might well bring about greater benefit than would

19 selective reduction in concentrations of other ambient criteria air pollutants. Furthermore, the

20 experimental studies of Utah Valley filter extracts point to PM-associated metals as a likely

21 cause or promoter of at least some of the health disorders associated with ambient PM. Beyond

22 this, available epidemiologic intervention studies do not yet give direct, quantitative evidence as

23 to the relative health benefits that would result from selective reduction of specific PM size

24 fractions. Also, these studies do not yet provide firm grounds for quantitative prediction of the

25 relative health benefits of single-pollutant reduction strategies vs. multi-pollutant reduction

26 strategies. Even in an almost ideal "natural experiment" such as Utah Valley, potentially

27 confounding factors other than ambient PM concentrations also changed during the steel mill

28 closure. These included concentrations of other pollutants and possible changes in population

29 due to out- and in-migration influenced by the closing and re-opening of the steel mill. While

30 changes in ambient PM concentrations undoubtedly played a role, other factors may also have

31 modified the size of the changes in health effects.

8.5 KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES

It is not possible to assign any absolute measure of certainty to conclusions based on the findings of the epidemiology studies discussed in this chapter. However, these observational study findings would be further enhanced by supportive findings of causal studies from other scientific disciplines (dosimetry, toxicology, etc.), in which other factors could be eliminated or controlled, as discussed in Chapters 6 and 7. The epidemiology studies discussed in this chapter demonstrate biologically-plausible responses in humans exposed at ambient concentrations. The most salient conclusions derived from the PM epidemiology studies include:

(1) A large and reasonably convincing body of epidemiology evidence confirms earlier associations between short- and long-term ambient PM_{10} exposures (inferred from stationary air monitor measures) and mortality/morbidity effects and suggest that PM_{10} (or one or more PM_{10} components) is a probable contributing cause of adverse human health effects.

(2) It is likely that there is significant spatial heterogeneity in the city-specific excess risk estimates for the relationships between short-term ambient PM_{10} concentrations and acute health effects. The reasons for such variation in effects estimates are not well understood at this time, but do not negate ambient PM's likely causative contribution to observed PM-mortality and/or morbidity associations in many locations. Possible factors contributing to the heterogeneity include geographic differences in air pollution mixtures, composition of PM components, and personal and sociodemographic factors affecting PM exposure (such as use of air conditioners, education, and so on).

(3) A growing body of epidemiology studies confirm associations between short- and long-term ambient $PM_{2.5}$ exposures (inferred from stationary air monitor measures) and adverse health effects and suggest that $PM_{2.5}$ (or one or more $PM_{2.5}$ components) is a probable contributing cause of observed PM-associated health effects. Some new epidemiology findings also suggest that health effects are associated with mass or number concentrations of ultrafine (nuclei-mode) particles, but not necessarily more so than for other ambient fine PM components.

1   (4)   A smaller body of evidence appears to support an association between short-term ambient
2   thoracic coarse fraction ($PM_{10-2.5}$) exposures (inferred from stationary air monitor measures)
3   and short-term health effects in epidemiology studies. This suggests that $PM_{10-2.5}$, or some
4   constituent component(s) of $PM_{10-2.5}$, may be a contributory cause of adverse health effects
5   in some locations. Reasons for differences among findings on coarse-particle health effects
6   reported for different cities are still poorly understood, but several of the locations where
7   significant $PM_{10-2.5}$ effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend
8   to be in drier climates and may have contributions to observed effects due to higher levels
9   of organic particles from biogenic processes (endotoxins, molds, etc.) during warm months.
10   Other studies suggest that coarse thoracic fraction ($PM_{10-2.5}$) particles of crustal origin are
11   generally unlikely to exert notable health effects under most ambient exposure conditions,
12   (however, see Item 14, below). Also, in some western U.S. cities where $PM_{10-2.5}$ is a large
13   part of PM_{10}, the relationship between hospital admissions and PM_{10} may be an indicator of
14   response to coarse thoracic particles from wood burning.
15   (5)   Long-term PM exposure durations, on the order of months to years, as well as on the order
16   of a few days, are statistically associated with serious human health effects (indexed by
17   mortality, hospital admissions/medical visits, etc.). More chronic PM exposures, on the
18   order of years or decades, appear to be associated with life shortening well beyond that
19   accounted for by the simple accumulation of the more acute effects of short-term PM
20   exposures (on the order of a few days). Some uncertainties remain regarding the magnitude
21   of and mechanisms underlying chronic health effects of long-term PM exposures and the
22   relationship between chronic exposure and acute responses to short-term exposure.
23   (6)   Recent investigations of the public health implications of such chronic PM exposure-
24   mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997)
25   found that relatively small differences in long-term exposure to airborne PM of ambient
26   origin can have substantial effects on life expectancy. For example, a calculation for the
27   1969-71 life table for U.S. white males indicated that a chronic exposure increase of
28   10 μg/m^3 PM was associated with a reduction of 1.31 years for the entire population's life
29   expectancy at age 25. Also, new evidence of associations of PM exposure with infant
30   mortality (Bobak and Leon, 1992, 1999; Woodruff et al., 1997; Loomis et al., 1999) and/or
31   intrauterine growth retardation (Dejmek et al., 1999) and consequent increase risk for many

1   serious health conditions associated with low birth weight, if further substantiated, would

2   imply that life shortening in the entire population from long-term PM exposure could well

3   be significantly larger than that estimated by Brunekreef (1997).

4   (7) Considerable coherence exists among effect size estimates for ambient PM health effects.

5   For example, results derived from several multi-city studies, based on pooled analyses of

6   data combined across multiple cities (thought to yield the most precise estimates of mean

7   effect size), show the percent excess total (non-accidental) deaths estimated per 50 μg/m^3

8   increase in 24-h PM_{10} to be: 2.3% in the 90 largest U.S. cities (4.5% in the Northeast U.S.

9   region); 3.4% in 10 large U.S. cities; 3.5% in the 8 largest Canadian cities; and 2.0% in

10   western European cities (using PM_{10} = TSP*0.55). These combined estimates are

11   consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD.

12   These and excess risk estimates from many other individual-city studies, generally falling

13   in the range of ca. 1.5 to 8.0% per 50 μg/m^3 24-h PM_{10} increment, also comport well with

14   numerous new studies confirming increased cause-specific cardiovascular- and respiratory-

15   related mortality. They are also coherent with larger effect sizes reported for cardiovascular

16   (in the range of ca. 3.0 to 10.0% per 50 μg/m^3 24-h PM_{10} increment) and respiratory (in the

17   range of ca. 5 to 25% per 50 μg/m^3 24-h PM_{10}) hospital admissions and visits, as would be

18   expected for these morbidity endpoints versus those for PM_{10}-related mortality.

19 (8) Several independent panel studies (but not all) that evaluated temporal associations

20   between PM exposures and measures of heart beat rhythm in elderly subjects provide

21   generally consistent indications of decreased heart rate variability (HRV) being associated

22   with ambient PM exposure (decreased HRV being an indicator of increased risk for serious

23   cardiovascular outcomes, e.g., heart attacks). Other studies point toward changes in blood

24   characteristics (e.g., C-reactive protein levels) related to increased risk of ischemic heart

25   disease also being associated with ambient PM exposures. However, these heart rhythm

26   and blood characteristics findings should currently be viewed as providing only limited or

27   preliminary support for PM-related cardiovascular effects.

28 (9) Notable new evidence now exists which substantiates positive associations between

29   ambient PM concentrations and increased respiratory-related hospital admissions,

30   emergency department, and other medical visits, particularly in relation to PM_{10} levels.

31   Of much interest are new findings tending to implicate not only fine particle components

1   but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of

2   asthma conditions. Also of much interest are emerging new findings indicative of likely

3   increased occurrence of chronic bronchitis in association with (especially chronic) PM

4   exposure. Also of particular interest are reanalyses or extensions of earlier prospective

5   cohort studies of long-term ambient PM exposure effects which demonstrate substantial

6   evidence for association of increased lung cancer risk with such PM exposures, especially

7   exposure to fine PM or its subcomponents.

8   (10) One major methodological issue affecting epidemiology studies of both short-term and

9   long-term PM exposure effects is that ambient PM of varying size ranges is typically found

10   in association with other air pollutants, including gaseous criteria pollutants (e.g, O_3, NO_2,

11   SO_2, CO), air toxics, and/or bioaerosols. Available statistical methods for assessing

12   potential confounding arising from these associations may not yet be fully adequate. The

13   inclusion of multiple pollutants often produces statistically unstable estimates. Omission of

14   other pollutants may incorrectly attribute their independent effects to PM. Second-stage

15   regression methods may have certain pitfalls that have not yet been fully evaluated. Much

16   progress in sorting out relative contributions of ambient PM components versus other

17   co-pollutants is nevertheless being made and, overall, tends to substantiate that observed

18   PM effects are at least partly due to ambient PM acting alone or in the presence of other

19   covarying gaseous pollutants. However, the statistical association of health effects with

20   PM acting alone or with other pollutants should not be taken as an indicator of a lack of

21   effect of the other pollutants. Indeed, the effects of the other pollutants may at times be

22   greater or less than the effects attributed to PM and may vary from place to place or from

23   time to time.

24   (11) It is possible that differences in observed health effects will be found to depend on site-

25   specific differences in chemical and physical composition characteristics of ambient

26   particles and on factors affecting exposure (such as air conditioning) as well as on

27   differences in PM mass concentration. For example, the Utah Valley study (Dockery et al.,

28   1999; Pope et al., 1991, 1999b) showed that PM_{10} particles, known to be richer in metals

29   during exposure periods while the steel mill was operating, were more highly associated

30   with adverse health effects than was PM_{10} during the PM exposure reduction while the steel

31   mill was closed. In contrast, PM_{10} or $PM_{2.5}$ was relatively higher in crustal particles during

1   windblown dust episodes in Spokane and in three central Utah sites than at other times, but

2   was not associated with higher total mortality. These differences require more research that

3   may become more feasible as the $PM_{2.5}$ sampling network produces air quality data related

4   to speciated samples.

5 (12) The above reasons suggest it is inadvisable to pool epidemiology studies at different

6   locations, different time periods, with different population sub-groups, or different health

7   endpoints, without assessing potential causes and the consequences of these differences.

8   Published multi-city analyses using common data bases, measurement devices, analytical

9   strategies, and extensive independent external review, as carried out in the APHEA and

10   NMMAPS studies are likely to be useful. Pooled analyses of more diverse collections of

11   independent studies of different cities, using varying methodology and/or data quality or

12   representativeness, are likely less credible and should not, in general, be used without

13   careful assessment of their underlying scientific comparability.

14 (13) It may be possible that different PM size components or particles with different

15   composition or sources produce effects by different mechanisms manifested at different

16   lags, or that different preexisting conditions may lead to different delays between exposure

17   and effect. Thus, although maximum effect sizes for PM effects have often been reported

18   for 0-1 day lags, evidence is also beginning to suggest that more consideration should be

19   given to lags of several days. Also, if it is considered that all health effects occurring at

20   different lag days are all real effects, so that the risks for each lag day should be additive,

21   then higher overall risks may exist that are higher than implied by maximum estimates for

22   any particular single or two-day lags. In that case, multi-day averages or distributed lag

23   models should be used.

24 (14) Certain classes of ambient particles may be distinctly less toxic than others and may not

25   exert human health effects at typical ambient exposure concentrations or only under special

26   circumstances. Coarse thoracic particles of crustal origin, for example, may be relatively

27   non-toxic under most circumstances compared to those of combustion origin such as wood

28   burning. However, crustal particles may be sufficiently toxic to cause human health effects

29   under some conditions; resuspended crustal particles, for example, may carry toxic trace

30   elements and other components from previously deposited fine PM, e.g., metals from

31   smelters (Phoenix) or steel mills (Steubenville, Utah Valley), PAH's from automobile

1   exhaust, or pesticides from administration to agricultural lands. Likewise, fine particles

2   from different sources have different effect sizes. More research is needed to identify

3   conditions under which one or another class of particles may cause little or no adverse

4   health effects, as well as conditions under which particles may cause notable effects.

5   (15) Certain epidemiology evidence suggests that reducing ambient PM_{10} concentrations may

6   reduce a variety of health effects on a time scale from a few days to a few months. This has

7   been found in epidemiology studies of "natural experiments" such as in the Utah Valley,

8   and by supporting toxicology studies using the particles from ambient community sampling

9   filters from the Utah Valley. Recent studies in Germany and in the Czech Republic also

10   tend to support a hypothesis that reductions in air pollution are associated with reductions

11   in the incidence of adverse health effects, but these studies cannot unambiguously attribute

12   improved health to reduced PM alone.

13   (16) Adverse health effects in children are emerging as a more important area of concern than in

14   the 1996 PM AQCD. Unfortunately, relatively little is known about the relationship of PM

15   to the most serious health endpoints (low birth weight, preterm birth, neonatal and infant

16   mortality, emergency hospital admissions and mortality in older children).

17   (17) Little is yet known about involvement of PM exposure in the progression from less serious

18   childhood conditions, such as asthma and respiratory symptoms, to more serious disease

19   endpoints later in life. This is an important health issue because childhood illness or death

20   may cost a very large number of productive life-years. Lastly, new epidemiologic studies

21   of ambient PM associations with increased non-hospital medical visits (physician visits)

22   and asthma effects suggest likely much larger health impacts and costs to society due to

23   ambient PM than just those indexed by mortality and/or hospital admissions/visits.

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REFERENCES

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995b) Estimating fine particulates less that 2.5 microns in aerodynamic diameter ($PM_{2.5}$) from airport visibility data in California. J. Exposure Anal. Environ. Epidemiol. 5: 161-180.

Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am. J. Respir. Crit. Care Med. 158: 289-298.

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. C.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1997) Lung function and long term exposure to air pollutants in Switzerland. Am. J. Respir. Crit. Care Med. 155: 122-129.

Alberdi Odriozola, J. C.; Díaz Jiménez, J.; Montero Rubio, J. C.; Mirón Pérez, I. J.; Pajares Ortíz, M. S.; Ribera Rodrigues, P. (1998) Air pollution and mortality in Madrid, Spain: a time-series analysis. Int. Arch. Occup. Environ. Health 71: 543-549.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Strachan, D. P. (1996) Air pollution and daily mortality in London: 1987-92. Br. Med. J. 312: 665-669.

Anderson, H. R.; Spix, C.; Medina, S.; Schouten, J. P.; Castellsague, J.; Rossi, G.; Zmirou, D.; Touloumi, G.; Wojtyniak, B.; Ponka, A.; Bacharova, L.; Schwartz, J.; Katsouyanni, K. (1997) Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur. Respir. J. 10: 1064-1071.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Emberlin, J.; Strachen, D. P. (1998) Air pollution, pollens, and daily admissions for asthma in London 1987-92. Thorax 53: 842-848.

Anderson, H. R.; Bremner, S. A.; Atkinson, R. W.; Harrison, R. M.; Walters, S. (2001) Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup. Environ. Med. 58: 504-510.

Archer, V. E. (1990) Air pollution and fatal lung disease in three Utah counties. Arch. Environ. Health 45: 325-334.

Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Ponce de Leon, A. (1999a) Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch. Environ. Health 54: 398-411.

Atkinson, R. W.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Bremner, S. A.; Ponce de Leon, A. (1999b) Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur. Respir. J. 13: 257-265.

Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.; Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2001) Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Am. J. Respir. Crit. Care Med. 164: 1860-1866.

Avol, E. L.; Gauderman, W. J.; Tan, S. M.; London, S. J.; Peters, J. M. (2001) Respiratory effects of relocating to areas of differing air pollution levels. Am. J. Respir. Crit. Care Med. 164: 2067-2072.

Awasthi, S.; Glick, H. A.; Fletcher, R. H.; Ahmed, N. (1996) Ambient air pollution & respiratory symptoms complex in preschool children. Indian J. Med. Res. 104: 257-262.

Bailey, D. L. R.; Clayton, P. (1982) The measurement of suspended particle and total carbon concentrations in the atmosphere using standard smoke shade methods. Atmos. Environ. 16: 2683-2690.

Baldi, I.; Tessier, J. F.; Kauffmann, F.; Jacqmin-Gadda, H.; Nejjari, C.; Salamon, R. (1999) Prevalence of asthma and mean levels of air pollution: results from the French PAARC survey. Eur. Respir. J. 14: 132-138.

Barbone, F.; Bovenzi, M.; Cavalleri, F.; Stanta, G. (1995) Air pollution and lung cancer in Trieste, Italy. Am. J. Epidemiol. 141: 1161-1169.

Basu, R.; Samet, J. M. (1999) A review of the epidemiological evidence on health effects of nitrogen dioxide exposure from gas stoves. J. Environ. Med. 1: 173-187.

Bateson, T. F.; Schwartz, J. (1999) Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. Epidemiology 10: 539-544.

Beckett, W. S. (2001) The air pollution detectives. Am. J. Respir. Crit. Care Med. 164: 515-516.

Beeson, W. L.; Abbey, D. E.; Knutsen, S. F. (1998) Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Environ. Health Perspect. 106: 813-823.

Berglund, D. J.; Abbey, D. E.; Lebowitz, M. D.; Knutsen, S. F.; McDonnell, W. F. (1999) Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest 115: 49-59.

Beyer, U.; Franke, K.; Cyrys, J.; Peters, A.; Heinrich, J.; Wichmann, H. E.; Brunekreef, B. (1998) Air pollution and respiratory health of children: the PEACE panel study in Hettstedt and Zerbst, Eastern Germany. Eur. Respir. Rev. 8: 61-69.

Blanchard, C. L.; Lurmann, F. W.; Roth, P. M.; Jeffries, H. E.; Korc, M. (1999) The use of ambient data to corroborate analyses of ozone control strategies. Atmos. Environ. 33: 369-381.

Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988. Lancet (8826): 1010-1014.

Bobak, M.; Leon, D. (1998) Air pollution and infant mortality: the effects are specific for respiratory causes in postneonatal period. Epidemiology 9: S58.

Bobak, M.; Leon, D. A. (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8. Occup. Environ. Med. 56: 539-543.

Bobak, M.; Roberts, A. (1997) Heterogeneity of air pollution effects is related to average temperature [letter]. Br. Med. J. 315: 1161.

Boezen, M.; Schouten, J.; Rijcken, B.; Vonk, J.; Gerritsen, J.; Van Der Zee, S.; Hoek, G.; Brunekreef, B.; Postma, D. (1998) Peak expiratory flow variability, bronchial responsiveness, and susceptibility to ambient air pollution in adults. Am. J. Respir. Crit. Care Med. 158: 1848-1854.

Boezen, H. M.; Van Der Zee, S. C.; Postma, D. S.; Vonk, J. M.; Gerritsen, J.; Hoek, G.; Brunekreef, B.; Rijcken, B.; Schouten, J. P. (1999) Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. Lancet 353: 874-878.

Borja-Aburto, V. H.; Loomis, D. P.; Bangdiwala, S. I.; Shy, C. M.; Rascon-Pacheco, R. A. (1997) Ozone, suspended particulates, and daily mortality in Mexico City. Am. J. Epidemiol. 145: 258-268.

Borja-Aburto, V. H.; Castillejos, M.; Gold, D. R.; Bierzwinski, S.; Loomis, D. (1998) Mortality and ambient fine particles in southwest Mexico City, 1993-1995. Environ. Health Perspect. 106: 849-855.

Braga, A. L. F.; Conceição, G. M. S.; Pereira, L. A. A.; Kishi, H. S.; Pereira, J. C. R.; Andrade, M. F.; Gonçalves, F. L. T.; Saldiva, P. H. N.; Latorre, M. R. D. O. (1999) Air pollution and pediatric respiratory hospital admissions in São Paulo, Brazil. J. Environ. Med. 1: 95-102.

Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2000) Do respiratory epidemics confound the association between air pollution and daily deaths? Eur. Respir. J. 16: 723-728.

Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001) The lag structure between particulate air pollution and respiratory and cardiovascular deaths in ten U.S. cities. J. Occup. Environ. Med. 43: 927-933.

Brauer, M.; Ebelt, S. T.; Fisher, T. V.; Brumm, J.; Petkau, A. J.; Vedal, S. (2001) Exposure of chronic obstructive pulmonary disease patients to particles: respiratory and cardiovascular health effects. J. Exposure Anal. Environ. Epidemiol. 11: 490-500.

Braun-Fahrländer, C.; Vuille, J. C.; Sennhauser, F. H.; Neu, U.; Künzle, T.; Grize, L.; Gassner, M.; Minder, C.; Schindler, C.; Varonier, H. S.; Wüthrich, B.; SCARPOL team. (1997) Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. Am. J. Respir. Crit. Care Med. 155: 1042-1049.

Bremner, S. A.; Anderson, H. R.; Atkinson, R. W.; McMichael, A. J.; Strachan, D. P.; Bland, J. M.; Bower, J. S. (1999) Short term associations between outdoor air pollution and mortality in London 1992-4. Occup. Environ. Med. 56: 237-244.

Brook, J. R.; Wiebe, A. H.; Woodhouse, S. A.; Audette, C. V.; Dann, T. F.; Callaghan, S.; Piechowski, M.; Dabek-Zlotorzynska, E.; Dloughy, J. F. (1997) Temporal and spatial relationships in fine particle strong acidity, sulphate, PM_{10}, and $PM_{2.5}$ across multiple Canadian locations. Atmos. Environ. 31: 4223-4236.

Brunekreef, B. (1997) Air pollution and life expectancy: is there a relation? Occup. Environ. Med. 54: 781-784.

Buffler, P. A.; Cooper, S. P.; Stinnett, S.; Contant, C.; Shirts, S.; Hardy, R. J.; Agu, V.; Gehan, B.; Burau, K. (1988) Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. Am. J. Epidemiol. 128: 683-699.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997a) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; Brook, J. R.; Yung, W. T.; Dales, R. E.; Krewski, D. (1997b) Association between ozone and hospitalization for respiratory diseases in 16 Canadian cities. Environ. Res. 72: 24-31.

Burnett, R. T.; Dales, R. E.; Brook, J. R.; Raizenne, M. E.; Krewski, D. (1997c) Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. Epidemiology 8: 162-167.

Burnett, R. T.; Cakmak, S.; Brook, J. R. (1998a) The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. Can. J. Public Health 89: 152-156.

Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.; Ozkaynak, H. (1998b) The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manage. Assoc. 48: 689-700.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54:130-139.

Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D. (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 15-39.

Burnett, R.; Ma, R.; Jerrett, M.; Goldberg, M. S.; Cakmak, S.; Pope, C. A., III; Krewski, D. (2001a) The spatial association between community air pollution and mortality: a new method of analyzing correlated geographic cohort data. Environ. Health Perspect. 109(suppl. 3): 375-380.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Raizenne, M. E.; Brook, J. R.; Dales, R. E.; Leech, J. A.; Cakmak, S.; Krewski, D. (2001b) Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. Am. J. Epidemiol. 153: 444-452.

Burton, R. M.; Suh, H. H.; Koutrakis, P. (1996) Spatial variation in particulate concentrations within metropolitan Philadelphia. Environ. Sci. Technol. 30: 400-407.

Cakmak, S.; Burnett, R. T.; Krewski, D. (1999) Methods for detecting and estimating population threshold concentrations for air pollution-related mortality with exposure measurement error. Risk Anal. 19: 487-496.

Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Chung, C. J.; Valencia, G.; Fordham, L. A.; García, R.; Osnaya, N.; Romero, L.; Acuña, H.; Villarreal-Calderón, A.; Devlin, R. B.; Koren, H. S. (2000) Exposure to air pollution is associated with lung hyperinflation in healthy children and adolescents in southwest Mexico City: a pilot study. Inhalation Toxicol. 12: 537-561.

Cassino, C.; Ito, K.; Bader, I.; Ciotoli, C.; Thurston, G.; Reibman, J. (1999) Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. Am. J. Respir. Crit. Care Med. 159: 1773-1779.

Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and mortality. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 61-72.

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

Chay, K. Y.; Greenstone, M. (2001) The impact of air pollution on infant mortality: evidence from geographic variation in pollution shocks induced by a recession. Berkeley, CA: University of California, Berkeley, Department of Economics. Available: http://elsa.berkeley.edu/users/kenchay/ [29 April, 2002].

Chen, C.; Chock, D. P.; Winkler, S. L. (1999) A simulation study of confounding in generalized linear models for air pollution epidemiology. Environ. Health Perspect. 107: 217-222.

Chen, L.; Yang, W.; Jennison, B. L.; Omaye, S. T. (2000) Air particulate pollution and hospital admissions for chronic obstructive pulmonary disease in Reno, Nevada. Inhalation Toxicol. 12: 281-298.

Chen, L.; Yang, W.; Jennison, B. L.; Goodrich, A.; Omaye, S. T. (2002) Air pollution and birth weight in northern Nevada, 1991-1999. Inhalation Toxicol. 14: 141-157.

Chew, F. T.; Goh, D. Y. T.; Ooi, B. C.; Saharom, R.; Hui, J. K. S.; Lee, B. W. (1999) Association of ambient air-pollution levels with acute asthma exacerbation among children in Singapore. Allergy (Copenhagen) 54: 320-329.

Chock, D. P.; Winkler, S.; Chen, C. (2000) A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J. Air Waste Manage. Assoc. 50: 1481-1500.

Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM_{10} air pollution. Arch. Environ. Health 52: 113-117.

Cifuentes, L. A.; Vega, J.; Köpfer, K.; Lave, L. B. (2000) Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J. Air Waste Manage. Assoc. 50: 1287-1298.

Clayton, C. A.; Perritt, R. L.; Pellizzari, E. D.; Thomas, K. W.; Whitmore, R. W.; Wallace, L. A.; Özkaynak, H.; Spengler, J. D. (1993) Particle total exposure assessment methodology (PTEAM) study: distributions of aerosol and elemental concentrations in personal, indoor, and outdoor air samples in a southern California community. J. Exposure Anal. Environ. Epidemiol. 3: 227-250.

Clench-Aas, J.; Bartonova, A.; Skjønsberg, O. H.; Leegaard, J.; Hagen, L. O.; Giæver, P.; Moseng, J.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE study in Oslo, Norway. Eur. Respir. Rev. 8: 36-43.

Clyde, M. A.; Guttorp, P.; Sullivan, E. (2000) Effects of ambient fine and coarse particles on mortality in Phoenix, Arizona. J. Exposure Anal. Environ. Epidemiol.: submitted.

Cohen, A. J. (2000) Outdoor air pollution and lung cancer. Environ. Health Perspect. 108(suppl. 4): 743-750.

Cohen, A. J.; Pope, C. A., III. (1995) Lung cancer and air pollution. Environ. Health Perspect. 103(suppl. 8): 219-224.

Conceição, G. M. S.; Miraglia, S. G. E. K.; Kishi, H. S.; Saldiva, P. H. N.; Singer, J. M. (2001) Air pollution and child mortality: a time-series study in São Paulo, Brazil. Environ. Health Perspect. 109(suppl. 3): 347-350.

Coull, B. A.; Schwartz, J.; Wand, M. P. (2001) Respiratory health and air pollution: additive mixed model analyses. Biostatistics 2: 337-349.

Coutant, R. W. (1977) Effect of environmental variables on collection of atmospheric sulfate. Environ. Sci. Technol. 11: 873-878.

Creason, J.; Neas, L.; Walsh, D.; Williams, R.; Sheldon, L.; Liao, D.; Shy, C. (2001) Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 PM study. J. Exposure Anal. Environ. Epidemiol. 11: 116-122.

Cropper, M. L.; Simon, N. B.; Alberini, A.; Arora, S.; Sharma, P. K. (1997) The health benefits of air pollution control in Delhi. Am. J. Agric. Econ. 79: 1625-1629.

Cuijpers, C. E. J.; Swaen, G. M. H.; Wesseling, G.; Wouters, E. F. M. (1994) Acute respiratory effects of summer smog in primary school children. Toxicol. Lett. 72: 227-235.

Dab, W.; Medina, S.; Quénel, P.; Le Moullec, Y.; Le Tertre, A.; Thelot, B.; Monteil, C.; Lameloise, P.; Pirard, P.; Momas, I.; Ferry, R.; Festy, B. (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50 (suppl. 1): S42-S46.

Damiá, A. D.; Fabregas, M. L.; Tordera, M. P.; Torrero, L. C. (1999) Effects of air pollution and weather conditions on asthma exacerbation. Respiration 66: 52-58.

Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am. J. Epidemiol. 152: 397-406.

Dejmek, J.; Selevan, S. G.; Benes, I.; Solansky, I.; Srám, R. J. (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. Environ. Health Perspect. 107: 475-480.

Delfino, R. J.; Coate, B. D.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Koutrakis, P. (1996) Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am. J. Respir. Crit. Care Med. 154: 633-641.

Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.

Delfino, R. J.; Murphy-Moulton, A. M.; Becklake, M. R. (1998) Emergency room visits for respiratory illnesses among the elderly in Montreal: association with low level ozone exposure. Environ. Res. 76: 67-77.

Dewanji, A.; Moolgavkar, S. H. (2000) A Poisson process approach for recurrent event data with environmental covariates. Environmetrics 11: 665-673.

Díaz, J.; García, R.; Ribera, P.; Alberdi, J. C.; Hernández, E.; Pajares, M. S.; Otero, A. (1999) Modeling of air pollution and its relationship with mortality and morbidity in Madrid, Spain. Int. Arch. Occup. Environ. Health 72: 366-376.

Dockery, D. W.; Spengler, J. D.; Neas, L. M.; Speizer, F. E.; Ferris, B. G., Jr.; Ware, J. H.; Brunekreef, B. (1989) An epidemiologic study of respiratory health status and indicators of indoor air pollution from combustion sources. In: Harper, J. P., ed. Combustion processes and the quality of the indoor environment: transactions of an international specialty conference; September 1988; Niagara Falls, NY. Pittsburgh, PA: Air & Waste Management Association; pp. 262-271. (A&WMA transactions series: TR-15).

Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. Environ. Res. 59: 362-373.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect. 104: 500-505.

Dockery, D. W.; Pope, C. A., III; Kanner, R. E.; Villegas, G. M.; Schwartz, J. (1999) Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. Cambridge, MA: Health Effects Institute; research report no. 83.

Dominici, F.; Samet, J. M.; Zeger, S. (2000a) Combining evidence on air pollution and daily mortality from the largest 20 US cities: a hierarchical modeling strategy. J. R. Stat. Soc. A 163: 263-302.

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

Dominici, F.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2002) Air pollution and mortality: estimating regional and national dose-response relationships. J. Am. Stat. Assoc. 97: 100-111.

Dye, J. A.; Lehmann, J. R.; McGee, J. K.; Winsett, D. W.; Ledbetter, A. D.; Everitt, J. I.; Ghio, A. J.; Costa, D. L. (2001) Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ. Health Perspect. 109(suppl. 3): 395-403.

Fairley, D. (1990) The relationship of daily mortality to suspended particulates in Santa Clara county, 1980-86. Environ. Health Perspect. 89: 159-168.

Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ. Health Perspect. 107: 637-641.

Forsberg, B.; Segerstedt, B.; Stjernberg, N.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Umeå, Sweden. Eur. Respir. Rev. 8: 12-19.

Frampton, M. W.; Ghio, A. J.; Samet, J. M.; Carson, J. L.; Carter, J. D.; Devlin, R. B. (1999) Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. Am. J. Physiol. 277: L960-L967.

Friedman, M. S.; Powell, K. E.; Hutwagner, L.; Graham, L. M.; Teague, W. G. (2001) Impact of changes in transportation and commuting behaviors during the 1996 summer olympic games in Atlanta on air quality and childhood asthma. JAMA J. Am. Med. Assoc. 285: 897-905.

Frischer, T.; Studnicka, M.; Gartner, C.; Tauber, E.; Horak, F.; Veiter, A.; Spengler, J.; Kühr, J.; Urbanek, R. (1999) Lung function growth and ambient ozone: a three-year population study in school children. Am. J. Respir. Crit. Care Med. 160: 390-396.

Fusco, D.; Forastiere, F.; Michelozzi, P.; Spadea, T.; Ostro, B.; Arca, M.; Perucci, C. A. (2001) Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur. Respir. J. 17: 1143-1150.

Gamble, J. L. (1998) Effects of ambient air pollution on daily mortality: a time series analysis of Dallas, Texas, 1990-1994. Presented at: 91st annual meeting and exhibition of the Air & Waste Management Association; June; San Diego, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 98-MP26.03.

Garcia-Aymerich, J.; Tobias, A.; Anto, J. M.; Sunyer, J. (2000) Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis. J. Epidemiol. Community Health 54: 73-74.

Garty, B. Z.; Kosman, E.; Ganor, E.; Berger, V.; Garty, L.; Wietzen, T.; Waisman, Y.; Mimouni, M.; Waisel, Y. (1998) Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. Ann. Allergy Asthma Immunol. 81: 563-570.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Gauvin, S.; Zmirou, D.; Pin, I.; Quentin, J.; Balducci, F.; Boudet, C.; Poizeau, D.; Brambilla, C. (1999) Short-term effect of exposure to suspended particulate matter (PM10) on the respiratory function of urban asthmatic and control adults. J. Environ. Med. 1: 71-79.

Gherghinova, M.; Kostyanve, S.; Ivanova, M. (1989) Theoretic values of body plethysmography indices in healthy children between 7 and 14 years of age. Pediatria 28: 52-58.

Ghio, A. J.; Devlin, R. B. (2001) Inflammatory lung injury after bronchial instillation of air pollution particles. Am. J. Respir. Crit. Care Med. 164: 704-708.

Gielen, M. H.; Van Der Zee, S. C.; Van Wijnen, J. H.; Van Steen, C. J.; Brunekreef, B. (1997) Acute effects of summer air pollution on respiratory health of asthmatic children. Am. J. Respir. Crit. Care Med. 155: 2105-2108.

Gold, D. R.; Damokosh, A. I.; Pope, C. A., III; Dockery, D. W.; McDonnell, W. F.; Serrano, P.; Retama, A.; Castillejos, M. (1999) Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. Epidemiology 10: 8-16.

Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. (2000) Ambient pollution and heart rate variability. Circulation 101: 1267-1273.

Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.; Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA: Health Effects Institute; research report 97. Available: http://www.healtheffects.org/pubs-research.htm [15 February, 2001].

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F. (2001a) The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 1. Nonaccidental mortality. Environ. Res. 86: 12-25.

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F.; Vincent, R. (2001b) The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 2. Cause-specific mortality. Environ. Res. 86: 26-36.

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Tamblyn, R.; Ernst, P.; Flegel, K.; Brook, J.; Bonvalot, Y.; Singh, R.; Valois, M.-F.; Vincent, R. (2001c) Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ. Health Perspect. 109(suppl. 4): 487-494.

Goldberg, M. S.; Burnett, R. T.; Brook, J.; Bailar, J. C., III; Valois, M.-F.; Vincent, R. (2001d) Associations between daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. Am. J. Epidemiol. 154: 817-826.

Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. Environ. Health Perspect. 104: 290-297.

Gouveia, N.; Fletcher, T. (2000) Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occup. Environ. Med. 57: 477-483.

Grievink, L.; Van der Zee, S. C.; Hoek, G.; Boezen, H. M.; Van't Veer, P.; Brunekreef, B. (1999) Modulation of the acute respiratory effects of winter air pollution by serum and dietary antioxidants: a panel study. Eur. Respir. J. 13: 1439-1446.

Güntzel, O.; Bollag, U.; Helfenstein, U. (1996) Asthma and exacerbation of chronic bronchitis: sentinel and environmental data in a time series analysis. Zentralbl. Hyg. Umweltmed. 198: 383-393.

Guo, Y. L.; Lin, Y.-C.; Sung, F.-C.; Huang, S.-L.; Ko, Y.-C.; Lai, J.-S.; Su, H.-J.; Shaw, C.-K.; Lin, R.-S.; Dockery, D. W. (1999) Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ. Health Perspect. 107: 1001-1006.

Gwynn, R. C.; Thurston, G. D. (2001) The burden of air pollution: impacts among racial minorities. Environ. Health Perspect. 109(suppl. 4): 501-506.

Gwynn, R. C.; Burnett, R. T.; Thurston, G. D. (2000) A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ. Health Perspect. 108: 125-133.

Hagen, J. A.; Nafstad, P.; Skrondal, A.; Bjørkly, S.; Magnus, P. (2000) Associations between outdoor air pollutants and hospitalization for respiratory diseases. Epidemiology 11: 136-140.

Hajat, S.; Haines, A.; Goubet, S. A.; Atkinson, R. W.; Anderson, H. R. (1999) Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. Thorax 54: 597-605.

Hajat, S.; Haines, A.; Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Emberlin, J. (2001) Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. Am. J. Epidemiol. 153: 704-714.

Haluszka, J.; Pisiewicz, K.; Miczynski, J.; Roemer, W.; Tomalak, W. (1998) Air pollution and respiratory health in children: the PEACE panel study in Kraków, Poland. Eur. Respir. Rev. 8: 94-100.

Harré, E. S. M.; Price, P. D.; Ayrey, R. B.; Toop, L. J.; Martin, I. R.; Town, G. I. (1997) Respiratory effects of air pollution in chronic obstructive pulmonary disease: a three month prospective study. Thorax 52: 1040-1044.

Harris, R. J. (1975) A primer of multivariate statistics. New York, NY: Academic Press; pp. 155-224.

Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. Arch. Environ. Health 49: 170-174.

Heinrich, J.; Hoelscher, B.; Wjst, M.; Ritz, B.; Cyrys, J.; Wichmann, H.-E. (1999) Respiratory diseases and allergies in two polluted areas in East Germany. Environ. Health Perspect. 107: 53-62.

Heinrich, J.; Hoelscher, B.; Wichmann, H. E. (2000) Decline of ambient air pollution and respiratory symptoms in children. Am. J. Respir. Crit. Care Med. 161: 1930-1936.

Henderson, B. E.; Gordon, R. J.; Menck, H.; SooHoo, J.; Martin, S. P.; Pike, M. C. (1975) Lung cancer and air pollution in southcentral Los Angeles County. Am. J. Epidemiol. 101: 477-488.

Hickey, R. J.; Boyce, D. E.; Harner, E. B.; Clelland, R. C. (1970) Ecological statistical studies on environmental pollution and chronic disease in metropolitan areas of the United States. Philadelphia, PA: Regional Science Research Institute. (RSRI discussion paper series no. 35).

Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.

Hiltermann, T. J. N.; de Bruijne, C. R.; Stolk, J.; Zwinderman, A. H.; Spieksma, F. Th. M.; Roemer, W.; Steerenberg, P. A.; Fischer, P. H.; van Bree, L.; Hiemstra, P. S. (1997) Effects of photochemical air pollution and allergen exposure on upper respiratory tract inflammation in asthmatics. Am. J. Respir. Crit. Care Med. 156: 1765-1772.

Hiltermann, T. J. N.; Stolk, J.; Van der Zee, S. C.; Brunekreef, B.; De Bruijne, C. R.; Fischer, P. H.; Ameling, C. B.; Sterk, P. J.; Hiemstra, P. S.; Van Bree, L. (1998) Asthma severity and susceptibility to air pollution. Eur. Respir. J. 11: 686-693.

Hoek, G.; Schwartz, J. D.; Groot, B.; Eilers, P. (1997) Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, the Netherlands. Arch. Environ. Health 52: 455-463.

Hoek, G.; Dockery, D. W.; Pope, A.; Neas, L.; Roemer, W.; Brunekreef, B. (1998) Association between PM_{10} and decrements in peak expiratory flow rates in children: reanalysis of data from five panel studies. Eur. Respir. J. 11: 1307-1311.

Hoek, G.; Brunekreef, B.; Verhoeff, A.; van, Wijnen, J.; Fischer, P. (2000) Daily mortality and air pollution in the Netherlands. J. Air Waste Manage. Assoc. 50: 1380-1389.

Hoek, G.; Brunekreef, B.; Fischer, P.; Van Wijnen, J. (2001) The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12: 355-357.

Hodgkin, J. E.; Abbey, D. E.; Euler, G. L.; Magie, A. R. (1984) COPD prevalence in nonsmokers in high and low photochemical air pollution areas. Chest 86: 830-838.

Hong, Y.-C.; Leem, J.-H.; Ha, E.-H.; Christiani, D. C. (1999) PM_{10} exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. Environ. Health Perspect. 107: 873-878.

Howel, D.; Darnell, R.; Pless-Mulloli, T. (2001) Children's respiratory health and daily particulate levels in 10 nonurban communities. Environ. Res. 87: 1-9.

Hrubá, F.; Fabiánová, E.; Koppová, K.; Vandenberg, J. J. (2001) Childhood respiratory symptoms, hospital admissions and long-term exposure to airborne particulate matter. J. Exposure Anal. Environ. Epidemiol. 11: 33-40.

Huang, Y.-L.; Batterman, S. (2000) Residence location as a measure of environmental exposure: a review of air pollution epidemiology studies. J. Exposure Anal. Environ. Epidemiol. 10: 66-85.

Ibald-Mulli, A.; Stieber, J.; Wichmann, H.-E.; Koenig, W.; Peters, A. (2001) Effects of air pollution on blood pressure: a population-based approach. Am. J. Public Health 91: 571-577.

Ilabaca, M.; Olaeta, I.; Campos, E.; Villaire, J.; Tellez-Rojo, M. M.; Romieu, I. (1999) Association between levels of fine particulate and emergency visits for pneumonia and other respiratory illnesses among children in Santiago, Chile. J. Air Waste Manage. Assoc. 49: 154-163.

Ito, K. (1990) An examination of the role of aerosol acidity in historical London, England daily mortality [dissertation]. Syracuse, NY: New York University. Available from: University Microfilms International, Ann Arbor, MI; AAD91-13012.

Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California, 1983-1992. Environ. Health Perspect. 105: 980-985.

Jalaludin, B. B.; Chey, T.; O'Toole, B. I.; Smith, W. T.; Capon, A. G.; Leeder, S. R. (2000) Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. Int. J. Epidemiol. 29: 549-557.

Jamason, P. F.; Kalkstein, L. S.; Gergen, P. J. (1997) A synoptic evaluation of asthma hospital admissions in New York City. Am. J. Respir. Crit. Care Med. 156: 1781-1788.

Janssen, N. A. H.; Van Vliet, P. H. N.; Aarts, F.; Harssema, H.; Brunekreef, B. (2001) Assessment of exposure to traffic related air pollution of children attending schools near motorways. Atmos. Environ. 35: 3875-3884.

Janssen, N. A. H.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as modifiers of the effect of PM_{10} on hospital admissions for heart and lung disease. Environ. Health Perspect. 110: 43-49.

Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpialek, Z. (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. J. Epidemiol. Commun. Health 44: 114-120.

Jedrychowski, W.; Flak, E. (1998) Separate and combined effects of the outdoor and indoor air quality on chronic respiratory symptoms adjusted for allergy among preadolescent children. Int. J. Occup. Med. Environ. Health 11: 19-35.

Jedrychowski, W.; Flak, E.; Mróz, E. (1999) The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ. Health Perspect. 107: 669-674.

Kalandidi, A.; Gratziou, C.; Katsouyanni, K.; Manalis, N.; Tzala, L.; Pantazopoulou, A.; Efthimiou, M.; Roussos, C.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Athens, Greece. Eur. Respir. Rev. 8: 117-124.

Katsouyanni, K.; Touloumi, G. (1998) Causes of regional differences in air pollution effects are being studied further [letter]. Br. Med. J. 316: 1982.

Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990) Air pollution and cause specific mortality in Athens. J. Epidemiol. Commun. Health 44: 321-324.

Katsouyanni, K.; Schwartz, J.; Spix, C.; Touloumi, G.; Zmirou, D.; Zanobetti, A.; Wojtyniak, B.; Vonk, J. M.; Tobias, A.; Pönkä, A.; Medina, S.; Bachárová, L.; Andersen, H. R. (1996) Short term effects of air pollution on health: a European approach using epidemiology time series data: the APHEA protocol. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S12-S18.

Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.; Sunyer, J.; Bachárová, L.; Schouten, J. P.; Pönkä, A.; Anderson, H. R. (1997) Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br. Med. J. 314: 1658-1663.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Gryparis, A.; Le Tertre, A.; Monopolis, Y.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12: 521-531.

Keatinge, W. R.; Donaldson, G. C. (2001) Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. Environ. Res. A 86: 209-216.

Keles, N.; Ilicali, Ö. C.; Deger, K. (1999) Impact of air pollution on prevalence of rhinitis in Istanbul. Arch. Environ. Health 54: 48-51.

Kelsall, J. E.; Samet, J. M.; Zeger, S. L.; Xu, J. (1997) Air pollution and mortality in Philadelphia, 1974-1988. Am. J. Epidemiol. 146: 750-762.

Kingham, S.; Briggs, D.; Elliott, P.; Fischer, P.; Lebret, E. (2000) Spatial variations in the concentrations of traffic-related pollutants in indoor and outdoor air in Huddersfield, England. Atmos. Environ. 34: 905-916.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling—interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. M., Jr.; Heilig, C. M.; Neas, L. M.; Dockery, D. W. (2000) Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. J. Air Waste Manage. Assoc. 50: 1215-1222.

Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.; Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter. Environ. Res. 63: 26-38.

Kontos, A. S.; Fassois, S. D.; Deli, M. F. (1999) Short-term effects of air pollution on childhood respiratory illness in Piraeus, Greece, 1987-1992: nonparametric stochastic dynamic analysis. Environ. Res. 81: 275-296.

Koren, H. S.; Utell, M. J. (1997) Asthma and the environment. Environ. Health Perspect. 105: 534-537.

Korrick, S. A.; Neas, L. M.; Dockery, D. W.; Gold, D. R.; Allen, G. A.; Hill, L. B.; Kimball, K. D.; Rosner, B. A.; Speizer, F. E. (1998) Effects of ozone and other pollutants on the pulmonary function of adult hikers. Environ. Health Perspect. 106: 93-99.

Kostianev, S.; Gerginova, M.; Ivanova, M. (1994) Reference values of lung function parameters in Bulgarian girls aged 7 to 14 years. Pediatria 33: 30-33.

Kotěšovec, F.; Vitnerova, N.; Leixner, M.; Benes, I.; Skorkovský, J.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Teplice, Czech Republic. Eur. Respir. Rev. 8: 70-77.

Kotěšovec, F.; Skorkovský, J.; Brynda, J.; Peters, A.; Heinrich, J. (2000) Daily mortality and air pollution in northern Bohemia; different effects for men and women. Cent. Eur. J. Public Health 8: 120-127.

Kousa, A.; Monn, C.; Rotko, T.; Alm, S.; Oblesby, L.; Jantunen, M. J. (2001) Personal exposures to NO_2 in the *EXPOLIS*-study: relation to residential indoor, outdoor and workplace concentrations in Basel, Helsinki and Prague. Atmos. Environ. 35: 3405-3412.

Krämer, U.; Behrendt, H.; Dolgner, R.; Ranft, U.; Ring, J.; Willer, H.; Schlipköter, H.-W. (1999) Airway diseases and allergies in East and West German children during the first 5 years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. Int. J. Epidemiol. 28: 865-873.

Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. H. (2000) Reanallysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.

Künzli, N.; Tager, I. B. (1997) The semi-individual study in air pollution epidemiology: a valid design as compared to ecologic studies. Environ. Health Perspect. 105: 1078-1083.

Künzli, N.; Ackermann-Liebrich, U.; Brändli, O.; Tschopp, J. M.; Schindler, C.; Leuenberger, P.; SAPALDIA Team. (2000) Clinically "small" effects of air pollution on FVC have a large public health impact. Eur. Respir. J. 15: 131-136.

Kwon, H.-J.; Cho, S.-H.; Nyberg, F.; Pershagen, G. (2001) Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology 12: 413-419.

Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108: 941-947.

Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.

Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.; Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2002) Short term effects of particulate air pollution on cardiovascular diseases in eight European cities. J. Epidemiol. Community Health: in press.

Lebowitz, M. D. (1971) A stimulus response method for the analysis of environmental and health events related in time. Environ. Lett. 2: 23-24.

Lebowitz, M. D.; Collins, L.; Holberg, C. J. (1987) Time series analyses of respiratory responses to indoor and outdoor environmental phenomena. Environ. Res. 43: 332-341.

Lee, J.-T.; Schwartz, J. (1999) Reanalysis of the effects of air pollution on daily mortality in Seoul, Korea: a case-crossover design. Environ. Health Perspect. 107: 633-636.

Lee, J.-T.; Shy, C. M. (1999) Respiratory function as measured by peak expiratory flow rate and PM_{10}: six communities study. J. Exposure Anal. Environ. Epidemiol. 9: 293-299.

Lee, R. E., Jr.; Caldwell, J. S.; Morgan, G. B. (1972) The evaluation of methods for measuring suspended particulates in air. Atmos. Environ. 6: 593-622.

Lee, J.-T.; Shin, D.; Chung, Y. (1999) Air pollution and daily mortality in Seoul and Ulsan, Korea. Environ. Health Perspect. 107: 149-154.

Lee, J.-T.; Kim, H.; Hong, Y.-C.; Kwon, H.-J.; Schwartz, J.; Christiani, D. C. (2000) Air pollution and daily mortality in seven major cities of Korea, 1991-1997. Environ. Res. 84: 247-254.

Leonardi, G. S.; Houthuijs, D.; Steerenberg, P. A.; Fletcher, T.; Armstrong, B.; Antova, T. (2000) Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of central Europe. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 1-14.

Levy, D. (1998) Fine particulate air pollution and out-of-hospital mortality in King County, Washington. In: Vostal, J. J., ed. Health effects of particulate matter in ambient air. Proceedings of an international conference; 1997; Prague, Czech Republic. Pittsburgh, PA: Air & Waste Management Association; pp. 262-271. (A&WMA publication VIP-80).

Levy, J. I.; Hammitt, J. K.; Spengler, J. D. (2000) Estimating the mortality impacts of particulate matter: what can be learned from between-study variability? Environ. Health Perspect. 108: 109-117.

Lewis, P. R.; Hensley, M. J.; Wlodarczyk, J.; Toneguzzi, R. C.; Westley-Wise, V. J.; Dunn, T.; Calvert, D. (1998) Outdoor air pollution and children's respiratory symptoms in the steel cities of New South Wales. Med. J. Aust. 169: 459-463.

Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. (1999) Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ. Health Perspect. 107: 521-525.

Lin, C. A.; Martins, M. A.; Farhat, S. C. L.; Pope, C. A., III; Conceição, G. M. S.; Anastácio, V. M.; Hatanaka, M.; Andrade, W. C.; Hamaue, W. R.; Böhm, G. M.; Saldiva, P. H. N. (1999) Air pollution and respiratory illness of children in São Paulo, Brazil. Paediatr. Perinat. Epidemiol. 13: 475-488.

Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Avol, E. L.; Hackney, J. D.; Gong, H., Jr. (1996) Short-term air pollution exposures and responses in Los Angeles area schoolchildren. J. Exposure Anal. Environ. Epidemiol. 6: 449-472.

Linn, W. S.; Gong, H., Jr.; Clark, K. W.; Anderson, K. R. (1999) Day-to-day particulate exposures and health changes in Los Angeles area residents with severe lung disease. J. Air Waste Manage. Assoc. 49: PM108-PM115.

Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ. Health Perspect. 108: 427-434.

Lipfert, F. W. (2000) The use and misuse of surrogate variables in environmental epidemiology. J. Environ. Med. 1: 267-278.

Lipfert, F. W.; Wyzga, R. E. (1999) Statistical considerations in determining the health significance of constituents of airborne particulate matter. J. Air Waste Manage. Assoc. 49: PM-182-191.

Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000a) Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J. Air Waste Manage. Assoc.: 1501-1513.

Lipfert, F. W.; Perry, H. M., Jr.; Miller, J. P.; Baty, J. D.; Wyzga, R. E.; Carmody, S. E. (2000b) The Washington University-EPRI veterans' cohort mortality study: preliminary results. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 41-73.

Lipfert, F. W.; Zhang, J.; Wyzga, R. E. (2000c) Infant mortality and air pollution: a comprehensive analysis of U.S. data for 1990. J. Air Waste Manage. Assoc. 50: 1350-1366.

Lippmann, M.; Thurston, G. D. (1996) Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations. J. Exposure Anal. Environ. Epidemiol. 6: 123-146.

Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no. 95.

Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County, California. Environ. Health Perspect. 105: 216-222.

Long, W.; Tate, R. B.; Neuman, M.; Manfreda, J.; Becker, A. B.; Anthonisen, N. R. (1998) Respiratory symptoms in a susceptible population due to burning of agricultural residue. Chest 113: 351-357.

Loomis, D.; Castillejos, M.; Gold, D. R.; McDonnell, W.; Borja-Aburto, V. H. (1999) Air pollution and infant mortality in Mexico City. Epidemiology 10: 118-123.

Lumley, T.; Heagerty, P. (1999) Weighted empirical adaptive variance estimators for correlated data regression. J. R. Stat. Soc. B 61(part 2): 459-477.

Lumley, T.; Sheppard, L. (2000) Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses. Environmetrics 11: 705-717.

Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.

Marcus, A. H.; Kegler, S. R. (2001) Confounding in air pollution epidemiology: when does two-stage regression identify the problem? Environ. Health Perspect. 109: 1193-1196.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.; Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern California children with asthma. Environ. Health Perspect. 107: 757-760.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Islam, T.; Gauderman, W. J.; Avol, E.; Margolis, H. G.; Peters, J. M. (2002) Asthma in exercising children exposed to ozone: a cohort study. Lancet 359: 386-391.

McDonnell, W. F.; Nishino-Ishikawa, N.; Petersen, F. F.; Chen, L. H.; Abbey, D. E. (2000) Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J. Exposure Anal. Environ. Epidemiol. 10: 427-436.

McGregor, G. R.; Walters, S.; Wordley, J. (1999) Daily hospital respiratory admissions and winter air mass types, Birmingham, UK. Int. J. Biometeorol. 43: 21-30.

Medina, S.; Le Tertre, A.; Quénel, P.; Le Moullec, Y.; Lameloise, P.; Guzzo, J. C.; Festy, B.; Ferry, R.; Dab, W. (1997) Air pollution and doctors' house calls: results from the ERPURS system for monitoring the effects of air pollution on public health in greater Paris, France, 1991-1995. Environ. Res. 75: 73-84.

Mendelsohn, R.; Orcutt, G. (1979) An empirical analysis of air pollution dose-response curves. J. Environ. Econ. Manage. 6: 85-106.

Michelozzi, P.; Forastiere, F.; Fusco, D.; Perucci, C. A.; Ostro, B.; Ancona, C.; Pallotti, G. (1998) Air pollution and daily mortality in Rome, Italy. Occup. Environ. Med. 55: 605-610.

Mills, P. K.; Abbey, D.; Beeson, W. L.; Petersen, F. (1991) Ambient air pollution and cancer in California Seventh-day Adventists. Arch. Environ. Health 46: 271-280.

Monn, C. (2001) Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmos. Environ. 35: 1-32.

Monn, Ch.; Carabias, V.; Junker, M.; Waeber, R.; Karrer, M.; Wanner, H. U. (1997) Small-scale spatial variability of particulate matter <10 µm (PM_{10}) and nitrogen dioxide. Atmos. Environ. 31: 2243-2247.

Moolgavkar, S. H. (2000a) Air Pollution and Mortality in Three U.S. Counties. Environ. Health Perspect. 108: 777-784.

Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.

Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.

Moolgavkar, S. H.; Luebeck, E. G. (1996) A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7: 420-428.

Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology 8: 364-370.

Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions for chronic respiratory disease in King County, Washington. In: Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 157-171.

Morgan, G.; Corbett, S.; Wlodarczyk, J.; Lewis, P. (1998) Air pollution and daily mortality in Sydney, Australia, 1989 through 1993. Am. J. Public Health 88: 759-764.

Morris, R. D. (2001) Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. Environ. Health Perspect. 109(suppl. 4): 495-500.

Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.

Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am. J. Public Health 85: 1361-1365.

Murray, C. J.; Nelson, C. R. (2000) State-space modeling of the relationship between air quality and mortality. J. Air Waste Manage. Assoc. 50: 1075-1080.

Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999) Healthy women's PEF variations with ambient summer concentrations of PM_{10}, $PM_{2.5}$, SO_4^{2-}, H^+, and O_3. Am. J. Respir. Crit. Care Med. 160: 117-125.

Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. Public Health Rep. 114: 135-148.

Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. Am. J. Epidemiol. 139: 1088-1099.

Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.

Neas, L. M.; Dockery, D. W.; Burge, H.; Koutrakis, P.; Speizer, F. E. (1996) Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. Am. J. Epidemiol. 143: 797-807.

Neas, L. M.; Schwartz, J.; Dockery, D. (1999) A case-crossover analysis of air pollution and mortality in Philadelphia. Environ. Health Perspect. 107: 629-631.

Neukirch, F.; Ségala, C.; Le Moullec, Y.; Korobaeff, M.; Aubier, M. (1998) Short-term effects of low-level winter pollution on respiratory health of asthmatic adults. Arch. Environ. Health 53: 320-328.

Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.

Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and stagnant air. Thorax 55: 466-470.

Nyberg, F.; Gustavsson, P.; Järup, L.; Bellander, T.; Berglind, N.; Jakobsson, R.; Pershagen, G. (2000) Urban air pollution and lung cancer in Stockholm. Epidemiology 11: 487-495.

Oglesby, L.; Rotko, T.; Krütli, P.; Boudet, C.; Kruize, H.; Jantunen, M. J.; Künzli, N. (2000) Personal exposure assessment studies may suffer from exposure-relevant selection bias. J. Exposure Anal. Environ. Epidemiol. 10: 251-266.

Ostro, B. (1995) Fine particulate air pollution and mortality in two Southern California counties. Environ. Res. 70: 98-104.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.

Ostro, B.; Chestnut, L.; Vichit-Vadakan, N.; Laixuthai, A. (1998) The impact of fine particulate matter in Bangkok, Thailand. In: Chow, J.; Koutrakis, P., eds. PM2.5: a fine particle standard. Volume II: proceedings of an international specialty conference; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 939-949. (A&WMA publication VIP-81).

Ostro, B. D.; Hurley, S.; Lipsett, M. J. (1999a) Air pollution and daily mortality in the Coachella Valley, California: a study of PM$_{10}$ dominated by coarse particles. Environ. Res. 81: 231-238.

Ostro, B. D.; Eskeland, G. S.; Sanchez, J. M.; Feyzioglu, T. (1999b) Air pollution and health effects: a study of medical visits among children in Santiago, Chile. Environ. Health Perspect. 107: 69-73.

Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, CA: a follow-up study. J. Exposure Anal. Environ. Epidemiol.: 10: 412-419.

Ostro, B.; Lipsett, M.; Mann, J.; Braxtron-Owens, H.; White, M. (2001) Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology 12: 200-208.

Osunsanya, T.; Prescott, G.; Seaton, A. (2001) Acute respiratory effects of particles: mass or number? Occup. Environ. Med. 58: 154-159.

Özkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal. 7: 449-461.

Ozkaynak, H.; Schatz, A. D.; Thurston, G. D.; Isaacs, R. G.; Husar, R. B. (1985) Relationships between aerosol extinction coefficients derived from airport visual range observations and alternative measures of airborne particle mass. J. Air Pollut. Control Assoc. 35: 1176-1185.

Özkaynak, H.; Xue, J.; Zhou, H.; Raizenne, M. (1996) Associations between daily mortality and motor vehicle pollution in Toronto, Canada. Boston, MA: Harvard University School of Public Health, Department of Environmental Health; March 25.

Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. (1995) Short-term effects of air pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. Environ. Res. 69: 31-36.

Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ. Res. 74: 24-33.

Pekkanen, J.; Brunner, E. J.; Anderson, H. R.; Tiittanen, P.; Atkinson, R. W. (2000) Daily concentrations of air pollution and plasma fibrinogen in London. Occup. Environ. Med. 57: 818-822.

Penttinen, P.; Timonen, K. L.; Tiittanen, P.; Mirme, A.; Ruuskanen, J.; Pekkanen, J. (2001) Number concentration and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. Environ. Health Perspect. 109: 319-323.

Pereira, L. A. A.; Loomis, D.; Conceição, G. M. S.; Braga, A. L. F.; Arcas, R. M.; Kishi, H. S.; Singer, J. M.; Böhm, G. M.; Saldiva, P. H. N. (1998) Association between air pollution and intrauterine mortality in São Paulo, Brazil. Environ. Health Perspect. 106: 325-329.

Perry, H. M., Jr.; Schnaper, H. W.; Meyer, G.; Swatzell, R. (1982) Clinical program for screening and treatment of hypertension in veterans. J. Natl. Med. Assoc. 74: 433-444.

Peters, A.; Goldstein, I. F.; Beyer, U.; Franke, K.; Heinrich, J.; Dockery, D. W.; Spengler, J. D.; Wichmann, H.-E. (1996) Acute health effects of exposure to high levels of air pollution in eastern Europe. Am. J. Epidemiol. 144: 570-581.

Peters, A.; Doring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349: 1582-1587.

Peters, A.; Dockery, D. W.; Heinrich, J.; Wichmann, H. E. (1997b) Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur. Respir. J. 10: 872-879.

Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997c) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.

Peters, A.; Kotesovec, F.; Skorkovsky, J.; Brynda, J.; Heinrich, J. (1999a) Akute Auswirkung der Schwebstaubkonzentrationen in der Außenluft auf die Mortalität - Vergleichsstudie Nordost-Bayern / Nordböhmen. Abschlußbericht [Acute effects of suspended particle concentrations in the atmosphere on mortality - a study comparing northeast Bavaria and north Bohemia. Final report]. Bavaria, Federal Republic of Germany: Institut für Epidemiologie; report no. GSF-EP S 1/99.

Peters, J. M.; Avol, E.; Navidi, W.; London, S. J.; Gauderman, W. J.; Lurmann, F.; Linn, W. S.; Margolis, H.; Rappaport, E.; Gong, H., Jr.; Thomas, D. C. (1999b) A study of twelve southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am. J. Respir. Crit. Care Med. 159: 760-767.

Peters, J. M.; Avol, E.; Gauderman, W. J.; Linn, W. S.; Navidi, W.; London, S. J.; Margolis, H.; Rappaport, E.; Vora, H.; Gong, H., Jr.; Thomas, D. C. (1999c) A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am. J. Respir. Crit. Care Med. 159: 768-775.

Peters, A.; Liu, E.; Verrier, R. L.; Schwartz, J.; Gold, D. R.; Mittleman, M.; Baliff, J.; Oh, J. A.; Allen, G.; Monahan, K.; Dockery, D. W. (2000a) Air pollution and incidence of cardiac arrhythmia. Epidemiology 11: 11-17.

Peters, A.; Fröhlich, M.; Döring, A.; Immervoll, T.; Wichmann, H.-E.; Hutchinson, W. L.; Pepys, M. B.; Koenig, W. (2000b) Particulate air pollution is associated with an acute phase response in men: results from the MONICA-Augsburg Study. Eur. Heart J.: in press.

Peters, A.; Dockery, D. W.; Muller, J. E.; Mittleman, M. A. (2001) Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103: 2810-2815.

Petroeschevsky, A.; Simpson, R. W.; Thalib, L.; Rutherford, S. (2001) Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch. Environ. Health 56: 37-52.

Pike, M. C.; Jing, J. S.; Rosario, I. P.; Henderson, B. E.; Menck, H. R. (1979) Occupation: "explanation" of an apparent air pollution related localized excess of lung cancer in Los Angeles County. In: Breslow, N. E.; Whitemore, A. S., eds. Energy and Health: proceedings of a conference sponsored by Siam Institute for Mathematics and Society; 1978; Alta, Utah. [SIAM-SIMS conference series 6].

Pless-Mulloli, T.; Howel, D.; King, A.; Stone, I.; Merefield, J.; Bessell, J.; Darnell, R. (2000) Living near opencast coal mining sites and children's respiratory health. Occup. Environ. Med. 57: 145-151.

Ponce de Leon, A.; Anderson, H. R.; Bland, J. M.; Strachan, D. P.; Bower, J. (1996) Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S63-S70.

Pönkä, A.; Savela, M.; Virtanen, M. (1998) Mortality and air pollution in Helsinki. Arch. Environ. Health 53: 281-286.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III; Kalkstein, L S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. Environ. Health Perspect. 104: 414-420.

Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM_{10} pollution: a daily time series analysis. Am. Rev. Respir. Dis. 144: 668-674.

Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM10 pollution in Utah valley. Arch. Environ. Health 47: 211-217.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999a) Particulate air pollution and daily mortality on Utah's Wasatch Front. Environ. Health Perspect. 107: 567-573.

Pope, C. A., III; Dockery, D. W.; Kanner, R. E.; Vollegas, G. M.; Schwartz, J. (1999b) Oxygen saturation, pulse rate, and particulate air pollution: a daily time-series panel study. Am. J. Respir. Crit. Care Med. 159: 365-372.

Pope, C. A., III; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas, G. M.; Gold, D. R.; Dockery, D. W. (1999c) Heart rate variability associated with particulate air pollution. Am. Heart J. 138: 890-899.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Prescott, G. J.; Cohen, G. R.; Elton, R. A.; Fowkes, F. G. R.; Agius, R. M. (1998) Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. Occup. Environ. Med. 55: 697-704.

Prescott, E.; Lange, P.; Vestbo, J.; Copenhagen City Heart Study Group. (1999) Socioeconomic status, lung function and admission to hospital for COPD: results from the Copenhagen City Heart Study. Eur. Respir. J. 13: 1109-1114.

Qian, Z. Chapman, R. S.; Tian, Q.; Chen, Y.; Lioy, P. J.; Zhang, J. (2000) Effects of air pollution on children's respiratory health in three Chinese cities. Arch. Environ. Health 55: 126-133.

Rahlenbeck, S. I.; Kahl, H. (1996) Air pollution and mortality in East Berlin during the winters of 1981-1989. Int. J. Epidemiol. 25: 1220-1226.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect. 104: 506-514.

Ransom, M. R.; Pope, C. A., III. (1992) Elementary school absences and PM10 pollution in Utah Valley. Environ. Res. 58: 204-219.

Rijnders, E.; Janssen, N. A.; Van Vliet, P. H.; Brunekreef, B. (2001) Personal and outdoor nitrogen dioxide concentrations in relation to degree of urbanization and traffic density. Environ. Health Perspect. 109(suppl. 3): 411-417.

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.; Fruin, S.; Chapa, G.; Shaw, G. M.; Harris, J. A. (2002) Ambient air pollution and risk of birth defects in southern California. Am. J. Epidemiol. 155: 17-25.

Rodes, C. E.; Holland, D. M. (1981) Variations of NO, NO_2 and O_3 concentrations downwind of a Los Angeles freeway. Atmos. Environ. 15: 243-250.

Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147: 118-124.

Roemer, W.; Hoek, G.; Brunekreef, B.; Haluszka, J.; Kalandidi, A.; Pekkanen, J. (1998) Daily variations in air pollution and respiratory health in a multicentre study: the PEACE project. Eur. Respir. J. 12: 1354-1361.

Roemer, W.; Hoek, G.; Brunekreef, B.; Clench-Aas, J.; Forsberg, B.; Pekkanen, J.; Schutz, A. (2000) PM_{10} elemental composition and acute respiratory health effects in European children (PEACE project). Eur. Respir. J. 15: 553-559.

Roemer, W. H.; Van Wijnen, J. H . (2001) Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology 12: 649-653.

Romieu, I.; Meneses, F.; Ruiz, S.; Sienra, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am. J. Respir. Crit. Care Med. 154: 300-307.

Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch. Environ. Health 52: 368-376.

Rooney, C.; McMichael, A. J.; Kovats, R. S.; Coleman, M. P. (1998) Excess mortality in England and Wales, and in greater London, during the 1995 heatwave. J. Epidemiol. Community Health 52: 482-486.

Roorda-Knape, M. C.; Janssen, N. A. H.; De Hartog, J. J.; Van Vliet, P. H. N.; Harssema, H.; Brunekreef, B. (1998) Air pollution from traffic in city districts near major motorways. Atmos. Environ. 32: 1921-1930.

Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderon, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy (Copenhagen) 53: 394-401.

Rossi, G.; Vigotti, M. A.; Zanobetti, A.; Repetto, F.; Gianelle, V.; and Schwartz, J. (1999) Air pollution and cause-specific mortality in Milan, Italy, 1980-1989. Arch. Environ. Health 54: 158-164.

Rothman, K. J.; Greenland, S., eds. (1998) Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

Rotko, T.; Koistinen, K.; Hänninen, O.; Jantunen, M. (2000) Sociodemographic descriptors of personal exposure to fine particles ($PM_{2.5}$) in *EXPOLIS* Helsinki. J. Exposure Anal. Environ. Epidemiol. 10: 385-393.

Rutherford, S.; Clark, E.; McTainsh, G.; Simpson, R.; Mitchell, C. (1999) Characteristics of rural dust events shown to impact on asthma severity in Brisbane, Australia. Int. J. Biometeorol. 42: 217-225.

Samet, J. M. (2000) What properties of particulate matter are responsible for health effects? In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 19-21.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996) Weather, air pollution and mortality in Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; review draft.

Samet, J.; Zeger, S.; Kelsall, J.; Xu, J.; Kalkstein, L. (1998) Does weather confound of modify the association of particulate air pollution with mortality? An analysis of the Philadelphia data, 1973-1980. Environ. Res. 77: 9-19.

Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000a) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000b) National morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Curriero, F. C.; Coursac, I.; Zeger, S. L. (2000c) Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N. Engl. J. Med. 343: 1742-1749.

Samoli, E.; Schwartz, J.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Bacharova, L.; Anderson, H. R.; Katsouyanni, K. (2001) Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. Environ. Health Perspect. 109: 349-353.

Sarnat, J. A.; Koutrakis, P.; Suh, H. H. (2000) Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J. Air Waste Manage. Assoc. 50: 1184-1198.

Sarnat, J. A.; Schwartz, J.; Catalano, P. J.; Suh, H. H. (2001) Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ. Health Perspect. 109: 1053-1061.

Scarlett, J. F.; Abbott, K. J.; Peacock, J. L.; Strachan, D. P.; Anderson, H. R. (1996) Acute effects of summer air pollution on respiratory function in primary school children in southern England. Thorax 51: 1109-1114.

Schouten, J. P.; Vonk, J. M.; de Graaf, A. (1996) Short term effects of air pollution on emergency hospital admissions for respiratory disease: results of the APHEA project in two major cities in The Netherlands, 1977-89. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S22-S29.

Schwartz, J. (1991) Particulate air pollution and daily mortality in Detroit. Environ. Res. 56: 204-213.

Schwartz, J. (1993) Air pollution and daily mortality in Birmingham, Alabama. Am. J. Epidemiol. 137: 1136-1147.

Schwartz, J. (1994) PM_{10}, ozone, and hospital admissions for the elderly in Minneapolis, MN. Arch. Environ. Health 49: 366-374.

Schwartz, J. (1995) Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50: 531-538.

Schwartz, J. (1997) Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377.

Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.

Schwartz, J. (2000a) Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ. Health Perspect. 108: 563-568.

Schwartz, J. (2000b) The distributed lag between air pollution and daily deaths. Epidemiology 11: 320-326.

Schwartz, J. (2000c) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151: 440-448.

Schwartz, J. (2000d) Daily deaths are associated with combustion particles rather than SO_2 in Philadelphia. Occup. Environ. Med. 57: 692-697.

Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. Environ. Health Perspect. 109(suppl. 3): 405-409.

Schwartz, J.; Dockery, D. W. (1992) Increased mortality in Philadelphia associated with daily air pollution concentrations. Am. Rev. Respir. Dis. 145: 600-604.

Schwartz, J.; Marcus, A. (1990) Mortality and air pollution in London: a time series analysis. Am. J. Epidemiol. 131: 185-194.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology. 11: 6-10.

Schwartz, J.; Zanobetti, A. (2000) Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 11: 666-672.

Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.

Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc. 46: 927-939.

Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; le Tertre, A.; Piekarksi, T.; Ponce de Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Schouten, J. P. (1996b) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S3-S11.

Schwartz, J.; Norris, G.; Larson, T.; Sheppard, L.; Claiborne, C.; Koenig, J. (1999) Episodes of high coarse particle concentrations are not associated with increased mortality. Environ. Health Perspect. 107: 339-342.

Schwartz, J.; Laden, F.; Zanobetti, A. (2002) The concentration-response relation between $PM_{2.5}$ and daily deaths. Environ. Health Perspect.: in press.

Seaton, A.; Soutar, A.; Crawford, V.; Elton, R.; McNerlan, S.; Cherrie, J.; Watt, M.; Agius, R.; Stout, R. (1999) Particulate air pollution and the blood. Thorax 54: 1027-1032.

Segala, C.; Fauroux, B.; Just, J.; Pascual, L.; Grimfeld, A.; Neukirch, F. (1998) Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. Eur. Respir. J. 11: 677-685.

Sheppard, L.; Damian, D. (2000) Estimating short-term PM effects accounting for surrogate exposure measurements from ambient monitors. Environmetrics 11: 675-687.

Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.

Shima, M.; Adachi, M. (1998) Indoor nitrogen dioxide in homes along trunk roads with heavy traffic. Occup. Environ. Med. 55: 428-433.

Shumway, R. H.; Tai, R. Y.; Tai, L. P.; Pawitan, Y. (1983) Statistical analysis of daily London mortality and associated weather and pollution effects. Sacramento, CA: California Air Resources Board; contract no. A1-154-33.

Shumway, R. H.; Azari, A. S.; Pawitan, Y. (1988) Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. Environ. Res. 45: 224-241.

Simpson, R. W.; Williams, G.; Petroeschevsky, A.; Morgan, G.; Rutherford, S. (1997) Associations between outdoor air pollution and daily mortality in Brisbane, Australia. Arch. Environ. Health 52: 442-454.

Smith, M. A.; Jalaludin, B.; Byles, J. E.; Lim, L.; Leeder, S. R. (1996) Asthma presentations to emergency departments in western Sydney during the January 2194 bushfires. Int. J. Epidemiol. 25: 1227-1236.

Smith, R. L.; Spitzner, D.; Kim, Y.; Fuentes, M. (2000) Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. J. Air Waste Manage. Assoc. 50: 1367-1379.

Soukup, J. M.; Ghio, A. J.; Becker, S. (2000) Soluble components of Utah Valley particulate pollution alter alveolar macrophage function in vivo and in vitro. Inhalation Toxicol. 12: 401-414.

Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Volksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E. (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. Environ. Health Perspect. 101: 518-526.

Spix, C.; Anderson, H. R.; Schwartz, J.; Vigotti, M. A.; LeTertre, A.; Vonk, J. M.; Touloumi, G.; Balducci, F.; Piekarski, T.; Bacharova, L.; Tobias, A.; Pönkä, A.; Katsouyanni, K. (1998) Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. Arch. Environ. Health 53: 54-64.

Stieb, D. M.; Burnett, R. T.; Beveridge, R. C.; Brook, J. R. (1996) Association between ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. Environ. Health Perspect. 104: 1354-1360.

Stieb, D. M.; Beveridge, R. C.; Rowe, B. H.; Walter, S. D.; Judek, S. (1998a) Assessing diagnostic classification in an emergency department: implications for daily time series studies of air pollution. Am. J. Epidemiol. 148: 666-670.

Stieb, D. M.; Brook, J. R.; Broder, I.; Judek, S.; Burnett, R. T.; Beveridge, R. C. (1998b) Personal exposure of adults with cardiorespiratory disease to particulate acid and sulfate in Saint John, New Brunswick, Canada. Appl. Occup. Environ. Hyg. 13: 461-468.

Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol.: 10: 461-477.

Sunyer, J.; Basagaña, X. (2001) Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. Int. J. Epidemiol. 30: 1138-1140.

Sunyer, J.; Spix, C.; Quénel, P.; Ponce-de-León, A.; Pönka, A.; Barumandzadeh, T.; Touloumi, G.; Bacharova, L.; Wojtyniak, B.; Vonk, J.; Bisanti, L.; Schwartz, J.; Katsouyanni, K. (1997) Urban air pollution and emergency admissions for asthma in four European cities: the APHEA project. Thorax 52: 760-765.

Sunyer, J.; Schwartz, J.; Tobias, A.; Macfarlane, D.; Garcia, J.; Anto, J. M. (2000) Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. Am. J. Epidemiol. 151: 50-56.

Taggart, S. C. O.; Custovic, A.; Francis, H. C.; Faragher, E. B.; Yates, C. J.; Higgins, B. G.; Woodcock, A. (1996) Asthmatic bronchial hyperresponsiveness varies with ambient levels of summertime air pollution. Eur. Respir. J. 9: 1146-1154.

Tam, A. Y. C.; Wong, C. M.; Lam, T. H.; Ong, S. G.; Peters, J.; Hedley, A. J. (1994) Bronchial responsiveness in children exposed to atmospheric pollution in Hong Kong. Chest 106: 1056-1060.

Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The human bone marrow response to acute air pollution caused by forest fires. Am. J. Respir. Crit. Care Med. 161: 1213-1217.

Tanaka, H.; Honma, S.; Nishi, M.; Igarashi, T.; Teramoto, S.; Nishio, F.; Abe, S. (1998) Acid fog and hospital visits for asthma: an epidemiological study. Eur. Respir. J. 11: 1301-1306.

Téllez-Rojo, M. M.; Romieu, I.; Ruiz-Velasco, S.; Lezana, M.-A.; Hernández-Avila, M. M. (2000) Daily respiratory mortality and PM10 pollution in Mexico City: importance of considering place of death. Eur. Respir. J. 16: 391-396.

Tenías, J. M.; Ballester, F.; Rivera, M. L. (1998) Association between hospital emergency visits for asthma and air pollution in Valencia, Spain. Occup. Environ. Med. 55: 541-547.

Thompson, A. J.; Shields, M. D.; Patterson, C. C. (2001) Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. Arch. Environ. Health 56: 234-241.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur. Respir. J. 13: 266-273.

Timonen, K. L.; Pekkanen, J. (1997) Air pollution and respiratory health among children with asthmatic or cough symptoms. Am. J. Respir. Crit. Care Med. 156: 546-552.

Tobias, A.; Campbell, M. J. (1999) Modelling influenza epidemics in the relation between black smoke and total mortality. A sensitivity analysis. J. Epidemiol. Community Health 53: 583-584.

Tolbert, P. E.; Klein, M.; Metzger, K. B.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2000a) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.

Tolbert, P. E.; Mulholland, J. A.; MacIntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.; Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000b) Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia. Am. J. Epidemiol. 151: 798-810.

Touloumi, G.; Katsouyanni, K.; Zmirou, D.; Schwartz, J.; Spix, C.; Ponce de Leon, A.; Tobias, A.; Quennel, P.; Rabczenko, D.; Bacharova, L.; Bisanti, L.; Vonk, J. M.; Ponka, A. (1997) Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Am. J. Epidemiol. 146: 177-185.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (1999) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Berkeley, CA: Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; report no. LBNL-43583.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

Turnovska, T.; Kostianev, S. (1999) Effects of reduced air pollution on children's pulmonary function. Cent. Eur. J. Public Health 7: 77-79.

U.S. Census Bureau. (1995) American housing survey for the United States in 1993. Washington, DC: U.S. Department of Commerce; current housing reports H150/93. Available: http://www.census.gov/hhes/www/housing/ahs/nationaldata.html [29 April, 2002].

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and PB95-124517.

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

U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants. Research Triangle Park, NC: Office of Research and Development; report nos. EPA/600/AP-93/004aF-cF. 3v. Available from: NTIS, Springfield, VA; PB96-185582, PB96-185590, and PB96-185608. Available online at: www.epa.gov/ncea/ozone.htm.

U.S. Environmental Protection Agency. (2000) Air quality criteria for carbon monoxide. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available: www.epa.gov/ncea/co/ [2000, October 6].

Van Der Zee, S. C.; Hoek, G.; Boezen, H. M.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (1999) Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms. Occup. Environ. Med. 56: 802-813.

Van Der Zee, S. C.; Hoek, G.; Boezen, M. H.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (2000) Acute effects of air pollution on respiratory health of 50-70 yr old adults. Eur. Respir. J. 15: 700-709.

Van Wijnen, J. H.; Van Der Zee, S. C. (1998) Traffic-related air pollutants: exposure of road users and populations living near busy roads. Rev. Environ. Health 13: 1-25.

Vasan, R. S.; Larson, M. G.; Leip, E. P.; Kannel, W. B.; Levy, D. (2001) Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 358: 1682-1686.

Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am. J. Respir. Crit. Care Med. 157: 1034-1043.

Vena, J. E. (1982) Air pollution as a risk factor in lung cancer. Am. J. Epidemiol. 116: 42-56.

Venn, A. J.; Lewis, S. A.; Cooper, M.; Hubbard, R.; Britton, J. (2001) Living near a main road and the risk of wheezing illness in children. Am. J. Respir. Crit. Care Med. 164: 2177-2180.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1967) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA J. Am. Med. Assoc. 202: 1028-1034.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1970) Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA J. Am. Med. Assoc. 213: 1143-1152.

Vigotti, M. A.; Rossi, G.; Bisanti, L.; Zanobetti, A.; Schwartz, J. (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. In: Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S71-S75.

Wallace, L. (1996) Indoor particles: a review. J. Air Waste Manage. Assoc. 46: 98-126.

Wang, B.; Peng, Z.; Zhang, X.; Xu, Y.; Wang, H.; Allen, G.; Wang, L.; Xu, X. (1999) Particulate matter, sulfur dioxide, and pulmonary function in never-smoking adults in Chongqing, China. Int. J. Occup. Environ. Health 5: 14-19.

Ward, D. J.; Miller, M. R.; Walters, S.; Harrison, R. M.; Ayres, J. G. (2000) Impact of correcting peak flow for nonlinear errors on air pollutant effect estimates from a panel study. Eur. Respir. J. 15: 137-140.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; Research Report no. 98.

Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.

Wjst, M.; Reitmeir, P.; Dold, S.; Wulff, A.; Nicolai, T.; Von Loeffelholz-Colberg, E. F.; Von Mutius, E. (1993) Road traffic and adverse effects on respiratory health in children. Br. Med. J. 307: 596-600.

Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental carbon. J. Air Pollut. Control Assoc. 33: 746-750.

Wong, C. M.; Lam, T. H.; Peters, J.; Hedley, A. J.; Ong, S. G.; Tam, A. Y. C.; Liu, J.; Spiegelhalter, D. J. (1998) Comparison between two districts of the effects of an air pollution intervention on bronchial responsiveness in primary school children in Hong Kong. J. Epidemiol. Community Health 52: 571-578.

Wong, C. M.; Hu, Z. G.; Lam, T. H.; Hedley, A. J.; Peters, J. (1999) Effects of ambient air pollution and environmental tobacco smoke on respiratory health of non-smoking women in Hong Kong. Int. J. Epidemiol. 28: 859-864.

Woodruff, T. J.; Grillo, J.; Schoendorf, K. C. (1997) The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. Environ. Health Perspect. 105: 608-612.

Wordley, J.; Walters, S.; Ayres, J. G. (1997) Short term variations in hospital admissions and mortality and particulate air pollution. Occup. Environ. Med. 54: 108-116.

Wu, W.; Samet, J. M.; Ghio, A. J.; Devlin, R. B. (2001) Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to Utah Valley PM. Am. J. Physiol. 281: L483-L489.

Xu, Z.; Yu, D.; Jing, L.; Xu, X. (2000) Air pollution and daily mortality in Shenyang, China. Arch. Environ. Health 55: 115-120.

Yang, W.; Jennison, B. L.; Omaye, S. T. (1997) Air pollution and asthma emergency room visits in Reno, Nevada. Inhalation Toxicol. 9: 15-29.

Ye, F.; Piver, W. T.; Ando, M.; Portier, C. J. (2001) Effects of temperature and air pollutants on cardiovascular and respiratory diseases for males and females older than 65 years of age in Tokyo, July and August 1980-1995. Environ. Health Perspect. 109: 355-359.

Yu, O.; Sheppard, L.; Lumley, T.; Koenig, J. Q.; Shapiro, G. G. (2000) Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ. Health Perspect. 108: 1209-1214.

Zanobetti, A.; Schwartz, J. (2000) Race, gender, and social status as modifiers of the effects of PM_{10} on mortality. J. Occup. Environ. Med. 42: 469-474.

Zanobetti, A.; Schwartz, J. (2001) Are diabetics more susceptible to the health effects of airborne particles? Am. J. Respir. Crit. Care Med. 164: 831-833.

Zanobetti, A.; Schwartz, J.; Dockery, D. W. (2000a) Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ. Health Perspect. 108: 1071-1077.

Zanobetti, A.; Wand, M. P.; Schwartz, J.; Ryan, L. M. (2000b) Generalized additive distributed lag models: quantifying mortality displacement. Biostatistics 1: 279-292.

Zeger, S. L.; Dominici, F.; Samet, J. (1999) Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10: 171-175.

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

Zeghnoun, A.; Beaudeau, P.; Carrat, F.; Delmas, V.; Boudhabhay, O.; Gayon, F.; Guincetre, D.; Czernichow, P. (1999) Air pollution and respiratory drug sales in the city of Le Havre, France, 1993-1996. Environ. Res. 81: 224-230.

Zeghnoun, A.; Czernichow, P.; Beaudeau, P.; Hautemanière, A.; Froment, L.; Le Tertre, A.; Quénel, P. (2001) Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995. Arch. Environ. Health 56: 327-335.

Zemp, E.; Elsasser, S.; Schindler, C.; Künzli, N.; Perruchoud, A. P.; Domenighetti, G.; Medici, T.; Ackermann-Liebrich, U.; Leuenberger, P.; Monn, C.; Bolognini, G.; Bongard, J.-P.; Brändli, O.; Karrer, W.; Keller, R.; Schöni, M. H.; Tschopp, J.-M.; Villiger, B.; Zellweger, J.-P.; SAPALDIA Team. (1999) Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). Am. J. Respir. Crit. Care Med. 159: 1257-1266.

Zhang, J.; Qian, Z.; Kong, L.; Zhou, L.; Yan, L.; Chapman, R. S. (1999) Effects of air pollution on respiratory health of adults in three Chinese cities. Arch. Environ. Health 54: 373-381.

Zhang, H.; Triche, E.; Leaderer, B. (2000) Model for the analysis of binary time series of respiratory symptoms. Am. J. Epidemiol. 151: 1206-1215.

Zmirou, D.; Schwartz, J.; Saez, M.; Zanobetti, A.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Ponce de León, A.; Le Moullec, Y.; Bacharova, L.; Schouten, J.; Pönkä, A.; Katsouyanni, K. (1998) Time-series analysis of air pollution and cause-specific mortality. Epidemiology 9: 495-503.

APPENDIX 8A

SHORT-TERM PM EXPOSURE-MORTALITY STUDIES: SUMMARY TABLE

TABLE 8A-1. SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States			
Samet et al. (2000a,b). 90 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 15.3 (Honolulu) to 52.0 (Riverside).	Non-accidental total deaths and cause-specific (cardiac, respiratory, and the other remaining) deaths, stratified in three age groups (<65, 65-75, 75+), were examined for their associations with PM_{10}, O_3, SO_2, NO_2, and CO (single, two, and three pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for the pollutants for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled within region. The third stage modeled between-region variation (7 regions). Two alternative assumptions were made regarding the prior distribution: one with possibly substantial heterogeneity and the other with less or no heterogeneity within region. The weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate; (3) socio-demographic variables; (4) urbanization; (5) variables related to measurement error.	The estimated city-specific coefficients were mostly positive at lag 0, 1, and 2 days (estimated overall effect size was largest at lag 1, with the estimated percent excess death rate per 10 $\mu g/m^3$ PM_{10} being about 0.5%). The posterior probabilities that the overall effects are greater than 0 at these lags were 0.99, 1.00, and 0.98, respectively. None of the county-specific variables (effect modifiers) in the second-stage regression significantly explained the heterogeneity of PM_{10} effects across cities. In the 3-stage regression model with the index for 7 geographical regions, the effect of PM_{10} varied somewhat across the 7 regions, with the effect in the Northeast being the greatest. Adding O_3 and other gaseous pollutants did not markedly change the posterior distributions of PM_{10} effects. O_3 effects, as examined by season, were associated with mortality in summer (≈ 0.5 percent per 10 ppb increase), but not in all season data (negative in winter).	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 2.3% (0.1, 4.5) for "more heterogeneity" across-city assumption; 2.2% (0.5, 4.0) for "less or no heterogeneity" across cities assumption. The largest PM_{10} effect estimated for 7 U.S. regions was for the Northeast: 4.6% (2.7, 6.5) excess deaths per 50 $\mu g/m^3$ PM_{10} increment.
Dominici et al. (2000). 20 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 23.8 $\mu g/m^3$ (San Antonio) to 52.0 $\mu g/m^3$ (Riverside).	Non-accidental total deaths (stratified in three age groups: <65, 65-75, 75+) were examined for their associations with PM_{10} and O_3 (single, 2, and 3 pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for PM_{10} and O_3 for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled as a function of city-specific covariates including mean PM_{10} and O_3 levels, percent poverty, and percent of population with age 65 and over. The prior distribution assumed heterogeneity across cities. To approximate the posterior distribution, a Markov Chain Monte Carlo (MCMC) algorithm with a block Gibbs sampler was implemented. The second stage also considered spatial model, in which RRs in closer cities were assumed to be more correlated.	Lag 1 day PM_{10} concentration positively associated with total mortality in most locations (only 2 out of 20 coefficients negative), though estimates ranged from 2.1% to –0.4% per 10 $\mu g/m^3$ PM_{10} increase. PM_{10} mortality associations changed little with the addition of O_3 to the model, or with the addition of a third pollutant in the model. The pattern of PM_{10} effects with respiratory and cardiovascular were similar to that of total mortality. The PM_{10} effect was smaller (and weaker) with other causes of deaths. The pooled analysis of 20 cities data confirmed the overall effect on total and cardiorespiratory mortality, with lag 1 day showing largest effect estimates. The posterior distributions for PM_{10} were generally not influenced by addition of other pollutants. In the data for which the distributed lags could be examined (i.e., nearly daily data), the sum of 7-day distributed lag coefficients was greater than each of single day coefficients. City-specific covariates did not predict the heterogeneity across cities. Regional model results suggested that PM_{10} effects in West U.S. were larger than in East and South.	Total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10}: 1.8 (–0.5, 4.1) for lag 0; 1.9 (–0.4, 4.3) for lag 1; 1.2 (–1.0, 3.4) for lag 2. Cardiovascular disease excess deaths per 50 $\mu g/m^3$ PM_{10}: 3.4 (1.0, 5.9).

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Braga et al. (2000). Five U.S. cities: Pittsburgh, PA; Detroit, MI; Chicago, IL; Minneapolis-St. Paul, MN; Seattle, WA. 1986-1993. PM_{10} means were 35, 37, 37, 28, and 33 $\mu g/m^3$, respectively in these cities.	Potential confounding caused by respiratory epidemics on PM-total mortality associations was investigated in a subset of the 10 cities evaluated by Schwartz (2000a,b), as summarized below. GAM Poisson models were used to estimate city-specific PM_{10} effects, adjusting for temperature, dewpoint, barometric pressure, time-trend and day-of-week. A cubic polynomial was used to for each epidemic period, and a dummy variable was used to control for isolated epidemic days. Average of 0 and 1 day lags were used.	When respiratory epidemics were adjusted for, small decreases in the PM_{10} effect were observed (9% in Chicago, 11% in Detroit, 3% in Minneapolis, 5% in Pittsburgh, and 15% in Seattle).	The overall estimated percent excess deaths per 50 $\mu g/m^3$ increase in PM_{10} was 4.3% (3.0, 5.6) before controlling for epidemics and 4.0% (2.6, 5.3) after. Average of 0 and 1 day lags.
Braga et al. (2001). Ten U.S. cities. Same as Schwartz (2000b).	The study examined the lag structure of PM_{10} effects on respiratory and cardiovascular cause-specific mortality. Using GAM Poisson model adjusting for temporal pattern and weather, three types of lag structures were examined: (1) 7-day unconstrained distributed lags; (2) 2-day average (0- and 1-day lag); and (3) 0-day lag. The results were combined across 10 cities.	The authors reported that respiratory deaths were more affected by air pollution levels on the previous days, whereas cardiovascular deaths were more affected by same-day pollution. Pneumonia, COPD, all cardiovascular disease, and myocardial infarction were all associated with PM_{10} in the three types of lags examined. The 7-day unconstrained lag model did not always give larger effect size estimates compared others.	In the 7-day unconstrained distributed lag model, the estimated percent excess deaths per 10ug/m3 PM_{10} were 2.7% (1.5, 2.9) , 1.7% (0.1, 3.3), 1.0% (0.6, 1.4), and 0.6% (0.0, 1.2) for pneumonia, COPD, all cardiovascular, and myocardial infarction mortality, respectively.
Schwartz (2000a). Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	Daily total (non-accidental) deaths (20, 19, 63, 60, 10, 133, 32, 6, 9, and 29, respectively in these cities in the order shown left). Deaths stratified by location of death (in or outside hospital) were also examined. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. The data were also analyzed by season (November through April as heating season). In the second stage, the PM_{10} coefficients were modeled as a function of city-dependent covariates including copollutant to PM_{10} regression coefficient (to test confounding), unemployment rate, education, poverty level, and percent non-white. Threshold effects were also examined. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	PM_{10} was significantly associated with total deaths, and the effect size estimates were the same in summer and winter. Adjusting for other pollutants did not substantially change PM_{10} effect size estimates. Also, socioeconomic variables did not modify the estimates. The effect size estimate for the deaths that occurred outside hospitals was substantially greater than that for inside hospitals. The effect size estimate was larger for subset with PM_{10} less than 50 $\mu g/m^3$.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.4 (2.7, 4.1); summer 3.4 (2.4, 4.4); winter 3.3 (2.3, 4.4); in-hospital 2.5 (1.5, 3.4); out-of-hospital 4.5 (3.4, 5.6); days < 50 $\mu g/m^3$ 4.4 (3.1, 5.7); with SO_2 2.9 (1.2, 4.6); with CO 4.6 (3.2, 6.0); with O_3 3.5 (1.6, 5.3).

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000b). Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	The issue of distributed lag effects was the focus of this study. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were examined using four models: (1) 1-day mean at lag 0 day; (2) 2-day mean at lag 0 and 1 day; (3) second-degree distributed lag model using lags 0 through 5 days; (4) unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	The effect size estimates for the quadratic distributed model and unconstrained distributed lag model were similar. Both distributed lag models resulted in substantially larger effect size estimates than the single day lag, and moderately larger effect size estimates than the two-day average models.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 3.3 (2.5, 4.1) for 1-day mean at lag 0; 5.4 (4.4, 6.3) 2-day mean of lag 0 and 1; 7.3 (5.9, 8.6) for quadratic distributed lag; and 6.6 (5.3, 8.0) for unconstrained distributed lag.
Schwartz and Zanobetti (2000). Ten U.S. cities. Same as above.	The issue of a threshold in PM-mortality exposure-response curve was the focus of this study. First, a simulation was conducted to show that the "meta-smoothing" could produce unbiased exposure-response curves. Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were used to generate mortality series in 10 cities, and GAM Poisson models were used to estimate exposure response curve. Effects of measurement errors were also simulated. In the analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature, dewpoint, and barometric pressure, and day-of-week. Smooth function of PM_{10} with the same span (0.7) in each of the cities. The predicted values of the log relative risks were computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the predicted values were combined across cities using inverse-variance weighting.	The simulation results indicated that the "meta-smoothing" approach did not bias the underlying relationships for the linear and threshold models, but did result in a slight downward bias for the logarithmic model. Measurement error (additive or multiplicative) in the simulations did not cause upward bias in the relationship below threshold. The threshold detection in the simulation was not very sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.	The combined exposure-response curve indicates that an increase of 50 $\mu g/m^3$ is associated with about a 4% increase in daily deaths. Avg. of 0 and 1 day lags.
Zanobetti and Schwartz (2000). Four U.S. cities: Chicago, IL; Detroit, MI; Minneapolis-St. Paul, MN; Pittsburgh, PA. 1986-1993. PM_{10} median = 33, 33, 25, and 31 respectively for these cities.	Separate daily counts of total non-accidental deaths, stratified by sex, race (black and white), and education (education > 12yrs or not), were examined to test hypothesis that people in each of these groups had higher risk of PM_{10}. GAM Poisson models adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were used. The mean of 0- and 1-day lag PM_{10} was used. The inverse variance weighted averages of the four cities' estimates were used to combine results.	The differences in the effect size estimates among the various strata were modest. The results suggest effect modification with the slope in female deaths one third larger than in male deaths. Potential interaction of these strata (e.g., black and female) were not investigated.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: white 5.0 (4.0, 6.0); black 3.9 (2.3, 5.4); male 3.8 (2.7, 4.9); female 5.5 (4.3, 6.7); education <12y 4.7 (3.3, 6.0); education > 12y 3.6 (1.0, 6.3).

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar (2000a) Cook County, Illinois Los Angeles County, CA Maricopa County, AZ 1987-1995 PM_{10}, CO, O_3, NO_2, SO_2 in all three locations. $PM_{2.5}$ in Los Angeles County. Cook Co: PM_{10} Median = 47 $\mu g/m^3$. Maricopa Co: PM_{10} Median = 41. Los Angeles Co: PM_{10} Median = 44; $PM_{2.5}$ Median = 22.	Associations between air pollution and time-series of daily deaths evaluated for three U.S. metropolitan areas with different pollutant mixes and climatic conditions. Daily total non-accidental deaths and deaths from cardiovascular disease (CVD), cerebrovascular (CrD), and chronic obstructive lung disease and associated conditions (COPD) were analyzed by generalized additive Poisson models in relation to 24-h readings for each of the air pollutants averaged over all monitors in each county. All models included an intercept term for day-of-week and a spline smoother for temporal trends. Effects of weather were first evaluated by regressing daily deaths (for each mortality endpoint) against temp and rel. humidity with lag times of 0 to 5 days. Then lags that minimized deviance for temp and rel. humidity were kept fixed for subsequent pollutant effect analyses. Each pollutant entered linearly into the regression and lags of between 0 to 5 days examined. Effects of two or more pollutants were then evaluated in multipollutant models. Sensitivity analyses were used to evaluate effect of degree of smoothing on results.	In general, the gases, especially CO (but not O_3) were much more strongly associated with mortality than PM. Specified pattern of results found for each county were as follows. For Cook Co., in single pollutant analyses PM_{10}, CO, and O_3 were all associated (PM_{10} most strongly on lag 0-2 days) with total mortality, as were SO_2 and NO_2 (strongest association on lag 1 day for the latter two). In joint analyses with one of gases, the coefficients for both PM_{10} and the gas were somewhat attenuated, but remained stat. sig. for some lags. With 3-pollutant models, PM_{10} coefficient became small and non-sig. (except at lag 0), whereas the gases dominated. For Los Angeles, PM_{10}, $PM_{2.5}$, CO, NO_2, and SO_2, (but not O_3), were all associated with total mortality. In joint analyses with CO or SO_2 and either PM_{10} or $PM_{2.5}$, PM metrics were markedly reduced and non-sig., whereas estimates for gases remained robust. In Maricopa Co. single-pollutant analyses, PM_{10} and each of the gases, (except O_3), were associated with total morality; in 2-pollutant models, coefficients for CO, NO_2, SO_2, were more robust than for PM_{10}. Analogous patterns of more robust gaseous pollutant effects were generally found for cause-specific (CVD, CrD, COPD) mortality analyses. Author concluded that while direct effect of individual components of air pollution cannot be ruled out, individual components best thought of as indices of overall pollutant mix.	In single pollutant models, estimated daily total mortality % excess deaths per 50 $\mu g/m^3$ PM_{10} was mainly in range of: 0.5-1.0% lags 0-2 Cook Co.; 0.25-1.0% lags 0-2 LA; 2.0% lag 2 Maricopa. Percent per 25 $\mu g/m^3$ $PM_{2.5}$ 0.5% lags 0, 1 for Los Angeles.

Maximum estimated COPD % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 5.4 (0.3,10.7), lag 2; with O_3, 3.0 (−1.8, 8.1) lag 2; LA 5.9 (−1.6, 14.0) lag 1; Maricopa 8.2 (−4.2, 22.3) lag 1; per 25 μg $PM_{2.5}$ in LA 2.7 (−3.4, 9.1).

CVD % per 50 $\mu g/m^3$ PM_{10}: Cook 2.2 (0.4, 4.1) lag 3; with O_3, SO_2 1.99 (−0.06, 4.1) lag 3; LA 4.5 (1.7, 7.4) lag 2; with CO −0.56 (−3.8, 2.8) lag 2; Maricopa 8.9 (2.7, 15.4) lag 1; with NO_2 7.4 (−0.95, 16.3) lag 1. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1; with CO 0.60 (−2.1, 3.4).

CrD % per 50 $\mu g/m^3$ PM_{10}: Cook 3.3 (−0.12, 6.8) lag 2; LA 2.9 (−2.3, 8.4) lag 3; Maricopa 11.1 (0.54, 22.8) lag 5. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 3.6 (−0.6, 7.9) lag 3. |

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ostro et al. (1999a). Coachella Valley, CA. 1989-1992. PM_{10} (beta-attenuation) Mean = 56.8 $\mu g/m^3$.	Study evaluated total, respiratory, cardiovascular, non-cardiorespiratory and age >50 yr deaths (mean = 5.4, 0.6, 1.8, 3.0, and 4.8 per day, respectively). The valley is a desert area where 50-60% of PM_{10} estimated to be coarse particles. Correlation between gravimetric and beta-attenuation, separated by 25 miles, was high (r = 0.93). Beta-attenuation data were used for analysis. GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used. Seasonally stratified analyses were also conducted. Lags 0-3 days (separately) of PM_{10} along with moving averages of 3 and 5 days examined, as were O_3, NO_2, and CO.	Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined, except non-cardiorespiratory series. The effect size estimates for total and cardiovascular deaths were larger for warm season (May through October) than for all year period. NO_2 and CO were significant predictor of mortality in single pollutant models, but in multi-pollutant models, none of the gaseous pollutants were significant (coefficients reduced), whereas PM_{10} coefficients remained the same and significant.	Total mortality percent excess deaths per 50 $\mu g/m^3$ PM_{10} at 2-day lag= 4.6 (0.6, 8.8). Cardiac deaths: 8.33 (2.14, 14.9) Respiratory deaths: 13.9 (3.25, 25.6)
Ostro et al. (2000). Coachella Valley, CA. 1989-1998. $PM_{2.5}$ = 16.8; $PM_{10-2.5}$ = 25.8 in Indio; $PM_{2.5}$ = 12.7; $PM_{10-2.5}$ = 17.9 in Palm Springs.	A follow-up study of the Coachella Valley data, with $PM_{2.5}$ and $PM_{10-2.5}$ data in the last 2.5 years. Both $PM_{2.5}$ and $PM_{10-2.5}$ were estimated for the remaining years to increase power of analyses.	Several pollutants were associated with all-cause mortality, including $PM_{2.5}$, CO, and NO_2. More consistent results were found for cardiovascular mortality, for which significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not $PM_{2.5}$ (possibly due to low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data).	Total percent excess deaths: PM_{10} = 2.0 (−1.0, 5.1) per 50 $\mu g/m^3$ $PM_{2.5}$ = 11.5 (0.2, 24.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 1.3 (−0.6, 3.5) per 25 $\mu g/m^3$ Cardio deaths: PM_{10} = 6.1 (2.0, 10.3) per 50 $\mu g/m^3$ $PM_{2.5}$ = 8.6 (−6.4, 25.8) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 2.6 (0.7, 4.5) per 25 $\mu g/m^3$ Respiratory deaths: PM_{10} = −2.0 (−11.4, 8.4) per 50 $\mu g/m^3$ $PM_{2.5}$ = 13.3 (−43.1, 32.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = −1.3 (−6.2, 4.0) per 25 $\mu g/m^3$

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Fairley (1999). Santa Clara County, CA 1989-1996. $PM_{2.5}$ (13); PM_{10} (34); $PM_{10-2.5}$ (11); COH (0.5 unit); NO_3 (3.0); SO_4 (1.8)	Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, COH, nitrate, sulfate, O_3, CO, NO_2, adjusting for trend, season, and min and max temperature, using Poisson GAM model. Season-specific analysis was also conducted. The same approach was also used to re-analyze 1980-1986 data (previously analyzed by Fairley, 1990).	$PM_{2.5}$ and nitrate were most significantly associated with mortality, but all the pollutants (except $PM_{10-2.5}$) were significantly associated in single poll. models. In 2 and 4 poll. models with $PM_{2.5}$ or nitrate, other pollutants were not significant. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that COH was very significantly associated with mortality.	Total mortality per 25 $\mu g/m^3$ $PM_{2.5}$ at 0 d lag: 8% in one pollutant model; 9-12% in 2 pollutant model; 12% in 4-pollutant model. Also, 8% per 50 $\mu g/m^3$ PM_{10} in one pollutant model and 2% per 25 $\mu g/m^3$ $PM_{10-2.5}$. Cardiovascular mortality: PM_{10} = 9% per 50 $\mu g/m^3$ $PM_{2.5}$ = 13% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 3% per 25 $\mu g/m^3$ Respiratory mortality: PM_{10} = 11% per 50 $\mu g/m^3$ $PM_{2.5}$ = 7% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 16% per 25 $\mu g/m^3$
Schwartz et al. (1999). Spokane, WA 1989-1995 PM_{10}: "control" days: 42 $\mu g/m^3$; dust-storm days: 263	Effects of high concentration of coarse crustal particles were investigated by comparing death counts on 17 dust storm episodes to those on non-episode days on the same day of the years in other years, adjusting for temperature, dewpoint, and day-of-week, using Poisson regression.	No association was found between the mortality and dust storm days on the same day or the following day.	0% (−4.5, 4.7) for dust storm days at 0 day lag (50 $\mu g/m^3$ PM_{10}) (lagged days also reported to have no associations).
Pope et al. (1999a). Ogden, Salt Lake City, and Provo/Orem, UT 1985-1995 PM_{10} (32 for Ogden; 41 for SLC; 38 for P/O)	Associations between PM_{10} and total, cardiovascular, and respiratory deaths studied in three urban areas in Utah's Wasatch Front, using Poisson GAM model and adjusting for seasonality, temperature, humidity, and barometric pressure. Analysis was conducted with or without dust (crustal coarse particles) storm episodes, as identified on the high "clearing index" days, an index of air stagnation.	Salt Lake City (SLC), where past studies reported little PM_{10}-mortality associations, had substantially more dust storm episodes. When the dust storm days were screened out from analysis and PM_{10} data from multiple monitors were used, comparable RRs were estimated for SLC and Provo/Orem (P/O).	Ogden PM_{10} Total (0 d) = 12.0% (4.5, 20.1) CVD (0-4 d) = 1.4% (−8.3, 12.2) Resp. (0-4 d) = 23.8 (2.8, 49.1) SLC PM_{10} Total (0 d) = 2.3% (0.47) CVD (0-4 d) = 6.5% (2.2, 11.0) Resp. (0-4 d) = 8.2 (2.4, 15.2) Provo/Ovem PM_{10} Total (0 d) = 1.9% (−2.1, 6.0) CVD (0-4 d) = 8.6% (2.4, 15.2) Resp. (0-4 d) = 2.2% (−9.8, 15.9) Note: Above % for $PM_{2.5}$ and $PM_{10-2.5}$ all per 25 $\mu g/m^3$; all PM_{10} % per 50 $\mu g/m^3$.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz and Zanobetti (2000). Chicago 1988-1993. PM$_{10}$. Median = 36 $\mu g/m^3$.	Total (non-accidental), in-hospital, out-of-hospital deaths (median = 132, 79, and 53 per day, respectively), as well as heart disease, COPD, and pneumonia elderly hospital admissions (115, 7, and 25 per day, respectively) were analyzed to investigate possible "harvesting" effect of PM$_{10}$. GAM Poisson models adjusting for temperature, relative humidity, day-of-week, and season were applied in baseline models using the average of the same day and previous day's PM$_{10}$. The seasonal and trend decomposition techniques called STL was applied to the health outcome and exposure data to decompose them into different time-scales (i.e, short-term to long-term), excluding the long, seasonal cycles (120 day window). The associations were examined with smoothing windows of 15, 30, 45, and 60 days.	The effect size estimate for deaths outside of the hospital is larger than for deaths inside the hospital. All cause mortality shows an increase in effect size at longer time scales. The effect size for deaths outside of hospital increases more steeply with increasing time scale than the effect size for deaths inside of hospitals.	Mortality RR estimates per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM$_{10}$: total deaths 4.5 (3.1, 6.0); in-hospital 3.9 (2.1, 5.8); out-of-hospital 6.3 (4.1, 8.6). For total deaths, the RR approximately doubles as the time scale changes from 15 days to 60 days. For out-of-hospital deaths, it triples from15 days to 60 days time scale.
Lippmann et al. (2000). Detroit, MI. 1992-1994. PM$_{10}$ = 31; PM$_{2.5}$ = 18; PM$_{10-2.5}$ = 13.	For 1992-1994 study period, total (non-accidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. The air pollution variables analyzed were: PM$_{10}$, PM$_{2.5}$, PM$_{10-2.5}$, sulfate, H$^+$, O$_3$, SO$_2$, NO$_2$, and CO.	PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H$^+$. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ effect size estimates were comparable per same distributional increment (5th to 95th percentile).	Total mortality percent excess deaths: PM$_{10}$ (1 d) = 4.4% ($-$1.0, 10.1) PM$_{2.5}$ (0 d) = 3.1% ($-$0.6, 7.0) PM$_{10-2.5}$ (1 d) = 4.0% ($-$1.2, 9.4) PM$_{10}$ (1 d) = 6.9% ($-$1.3, 15.7) PM$_{2.5}$ (1 d) = 3.2% ($-$2.3, 8.9) PM$_{10-2.5}$ (1 d) = 7.8% (0.0, 16.2)
For 1985-1990 period TSP, PM$_{10}$, TSP-PM$_{10}$, Sulfate from TSP (TSP-SO$_4^=$)	For earlier 1985-1990 study period, total non-accidental, circulatory, respiratory, and "other" (non-circulatory or respiratory non-accidental) mortality were evaluated versus noted PM indices and gaseous pollutants.	Both PM$_{10}$ (lag 1 and 2 day) and TSP (lag 1 day) but not TSP-PM$_{10}$ or TSP-SO$_4^=$ significantly associated with respiratory mortality for 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM$_{10}$ or TSP reduced PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.	Respiratory mortality: PM$_{10}$ (0 d) = 7.8% ($-$10.2, 29.5) Circulatory mortality: PM$_{2.5}$ (o d) = 2.3% ($-$10.3, 16,6) PM$_{10-25}$ (2 d) = 7.4% ($-$9.1, 26.9) Note: All above PM$_{10}$ per 50 $\mu g/m^3$; all PM$_{2.5}$ and PM$_{10-2.5}$ % per 25 $\mu g/m^3$.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Chock et al. (2000). 1989-1991 Pittsburgh, PA PM_{10} (daily) $PM_{2.5}$ (every 2 days)	Study evaluated associations between daily mortality and several air pollution variables (PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2) in two age groups (<75 yr., ≥75 yr.) in Pittsburgh, PA, during 3-yr. period. Poisson regression used, including filtering of data based on cubic B-spline basis functions, with adjustments for seasonal trends, day-of-week effects, temp., dew point. Single- and multi-pollutant models run for 0, 1, 2, and 3 day lags. $PM_{2.5}/PM_{10} \approx 0.67$.	Issues of seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients emphasized. Single- and multi-pollutant non-seasonal models show significant positive association between PM_{10} and daily mortality, but seasonal models showed much multi-collinearity, masking association of any pollutant with mortality. Also, based on data set half the size for PM_{10}, the $PM_{2.5}$ coefficients were highly unstable and, since no consistently significant associations found in this small data set stratified by age group and season, no conclusions drawn on relative role of $PM_{2.5}$ vs. $PM_{10-2.5}$.	Total mortality percent increase per 25 $\mu g/m^3$ for aged <75 yrs: $PM_{2.5}$ = 2.6% (2.0, 7.3) $PM1_{0-2.5}$ = 0.7% (−1.7, 3.7) Total mortality percent increase per 25 $\mu g/m^3$ for aged >75 yrs: $PM_{2.5}$ = 1.5% (−3.0, 6.3) $PM1_{0-2.5}$ = 1.3% (−1.3, 3.8)
Klemm and Mason (2000). Atlanta, GA 1998-1999 $PM_{2.5}$ mean=19.9; $PM_{2.5}/PM_{10}$ =0.65. Nitrate, EC, OC, and oxygenated HC.	Reported "interim" results for 1 yr period of observations regarding total mortality in Atlanta, GA during 1998-1999. Generalized additive model used to assess effects of $PM_{2.5}$ vs $PM_{10-2.5}$, and for nitrate, EC, OC and oxygenated HC components.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.	Total mortality percent increase per 25 $\mu g/m^3$ for: $PM_{2.5}$ = 4.8% (−3.2, 13.4) $PM1_{0-2.5}$ = 1.4% (−11.3, 15.9)
Gwynn et al. (2000). Buffalo, N.Y. 1988-1990. PM_{10} (24); COH (0.2 /1000ft); SO_4= (62 nmoles/m3)	Total, circulatory, and respiratory mortality and unscheduled hospital admissions were analyzed for their associations with H+, SO_4=, PM_{10}, COH, O_3, CO, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, humidity, using. Poisson and negative binomial GAM models.	For total mortality, all the PM components were significantly associated, with H+ being the most significant, and COH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality.	12% (2.6, 22.7) per 50 $\mu g/m^3$ PM_{10} at 2-day lag.
Schwartz (2000c). Boston, MA. 1979-1986. $PM_{2.5}$ mean = 15.6.	Non-accidental total, pneumonia, COPD, and ischemic heart disease mortality were examined for possible "harvesting" effects of PM. The mortality, air pollution, and weather time-series were separated into seasonal cycles (longer than 2-month period), midscale, and short-term fluctuations using STL algorithm. Four different midscale components were used (15, 30, 45, and 60 days) to examine the extent of harvesting. GAM Poisson regression analysis was performed using deaths, pollution, and weather for each of the four midscale periods.	For COPD deaths, the results suggest that most of the mortality was displaced by only a few months. For pneumonia, ischemic heart disease, and total mortality, the effect size increased with longer time scales.	Total mortality percent increase per 25 $\mu g/m^3$ increase in $PM_{2.5}$: 5.3 (1.8, 9.0) for short-term fluctuations; 9.6 (8.1, 11.1) for the 60 day window.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Lipfert et al. (2000a). Philadelphia (7 county Metropolitan area), 1992-1995. Harvard PM measurements: $PM_{2.5}$ (17.3); PM_{10} (24.1); $PM_{10-2.5}$ (6.8), sulfate (53.1 nmol/m3); H^+ (8.0 nmol/m3).	12 mortality variables, as categorized by area, age, and cause, were regressed on 29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by sub-areas), yielding 348 regression results. Both dependent and explanatory variables were pre-filtered using the19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for hot and cold days and day-of-week using stepwise procedure. The average of current and previous days' pollution levels were used.	Significant associations were found for a wide variety gaseous and particulate pollutants, especially for peak O_3. No systematic differences were seen according particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.	The fractional Philadelphia mortality risk attributed to the pollutant levels: "average risk" was 0.0423 for 25 $\mu g/m^3$ $PM_{2.5}$; 0.0517 for 25 $\mu g/m^3$ $PM_{10-2.5}$; 0.0609 for 50 $\mu g/m^3$ PM_{10}, using the Harvard PM indices at avg. of 0 and 1 d lags.
Laden et. al. (2000) Six Cities (means): Watertown, MA (16.5); Kingston-Harriman, TN (21.1); St. Louis, MO (19.2); Steubenville, OH (30.5); Portage, WI (11.3); Topeka, KS (12.2). 1979-1988?. 15 trace elements in the dichot $PM_{2.5}$: Si, S, Cl, K, Ca, V, Mn, Al, Ni, Zn, Se, Br, Pb, Cu, and Fe.	Total (non-accidental), ischemic heart disease, pneumonia, and COPD (mean daily total deaths for the six cities: 59, 12, 55, 3, 11, and 3, respectively in the order shown left). A factor analysis was conducted on the 15 elements in the fine fraction of dichot samplers to obtain five common factors; factors were rotated to maximize the projection of the single "tracer" element (as in part identified from the past studies conducted on these data) for each factor; $PM_{2.5}$ was regressed on the identified factors scores so that the factor scores could be expressed in the mass scale. Using GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time, mortality was regressed on the factor scores in the mass scale. The mean of the same-day and previous day (increasing the sample size from 6,211 to 9,108 days) mass values were used. The city-specific regression coefficients were combined using inverse variance weights.	Three sources of fine particles were defined in all six cities with a representative element for each source type: Si for soil and crustal material; Pb for motor vehicle exhaust; and Se for coal combustion sources. In city-specific analysis, additional sources (V for fuel oil combustion, Cl for salt, etc.) were considered. Five source factors were considered for each city, except Topeka with the three sources. Coal and mobile sources account for the majority of fine particles in each city. In all of the metropolitan areas combined, 46% of the total fine particle mass was attributed to coal combustion and 19% to mobile sources. The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality.	Total mortality percent excess overall: 4.0 (2.8, 5.3), 2.7 (0.6, 5.0) with each 25 $\mu g/m^3$ increase in the two-day mean of coal combustion fine PM factor; 8.7 (4.2, 13.4) with each 25 $\mu g/m^3$ increase in the two-day mean of mobile source fine PM factor; −5.7 (−13.7, 3.2) with each 25 $\mu g/m^3$ increase in the two-day mean of the crustal source fine PM factor.
Levy (1998). King County, WA. 1990-1994. PM_{10} Nephelometer (30); (0.59 bsp unit)	Out-of-hospital deaths (total, respiratory, COPD, ischemic heart disease, heart failure, sudden cardiac death screening codes, and stroke) were related to PM_{10}, nephelometer (0.2 - 1.0 μm fine particles), SO_2, and CO, adjusting for day-of-week, month of the year, temperature and dewpoint, using Poisson regression.	Nephelometer data were not associated with mortality. Cause-specific death analyses suggest PM associations with ischemic heart disease deaths. Associations of mortality with SO_2 and CO not mentioned. Mean daily death counts were small (e.g., 7.7 for total; 1.6 for ischemic heart disease). This is an apparently preliminary analysis.	Total mortality percent excess: 5.6% (−2.4, 1.43) per 50 $\mu g/m^3$ PM_{10} at avg. of 2 to 4 d lag; 7.2% (−6.3, 22.8) with SO_2 CO. 1.8% (−3.5, 7.3) per 25 $\mu g/m^3$ PM_1; −1.0 (−8.7,. 7.7) with SO_2 and CO.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Mar et al. (2000). Phoenix, AZ. 1995-1997. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (TEOM), with means = 46.5, 13.0, and 33.5, respectively; and $PM_{2.5}$ (DFPSS), mean = 12.0.	Total (non-accidental) and cardiovascular deaths (mean = 8.6 and 3.9, respectively) for only those who resided in the zip codes located near the air pollution monitor were included. GAM Poisson models were used, adjusting for season, temperature, and relative humidity. Air pollution variables evaluated included: O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days evaluated. Factor analysis also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores included in mortality regression.	Total mortality was significantly associated with CO and NO_2 and weakly associated with SO_2, PM_{10}, $PM_{10-2.5}$, and EC. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, OC and EC. Combustion-related factors and secondary aerosol factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality.	Total mortality percent excess: 5.4 (0.1, 11.1) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 3.0 (−0.5, 6.6) for $PM_{10-2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d; 3.0 (−0.7, 6.9) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d. Cardiovascular mortality RRs: 9.9 (1.9, 18.4) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 18.7 (5.7, 33.2) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 1 d; and 6.4 (1.4, 11.7) PM_{10} (TEOM) 25 $\mu g/m^3$ $PM_{10-2.5}$ at lag 0 d.
Clyde et al. (2000). Phoenix, AZ. 1995-1998. PM_{10}, and $PM_{2.5}$, (from TEOM), with means = 45.4, and 13.8. $PM_{10-2.5}$ computed as PM_{10}-$PM_{2.5}$.	Elderly (age ≥65 years) non-accidental mortality for three regions of increasing size in Phoenix urban area analyzed to evaluate influence of spatial uniformity of PM_{10} and $PM_{2.5}$. All-age accidental deaths for the metropolitan area also examined as a "control". GAM Poisson models adjusting for season (smoothing splines of days), temperature, specific humidity, and lags 0- to 3-d of weather variables. PM indices for lags 0-3 d considered. Bayesian Model Averaging (BMA) produces posterior mean relative risks by weighting each model (out of all possible model specifications examined) based on support received from the data.	The BMA results suggest that a weak association was found only for the mortality variable defined over the region with uniform $PM_{2.5}$, with a 0.91 probability that RR is greater than 1. The other elderly mortality variables, including the accidental deaths ("control"), had such probabilities in the range between 0.46 to 0.77. Within the results for the mortality defined over the region with uniform $PM_{2.5}$, the results suggested that effect was primarily due to coarse particles rather than fine; only the lag 1 coarse PM was consistently included in the highly ranked models.	Posterior mean RRs and 90% probability intervals per changes of 25 $\mu g/m^3$ in all lags of fine and coarse PM for elderly mortality for uniform PM_{10} region: 1.06 (1+, 1.11).

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Smith et al. (2000). Phoenix, AZ. 1995-1997	Study evaluated effects of daily and 2- to 5-day average coarse ($PM_{10\text{-}2.5}$) and fine ($PM_{2.5}$) particles from an EPA-operated central monitoring site on nonaccidental mortality among elderly (65+ years), using time-series analyses for residents within city of Phoenix and, separately, for region of circa 50 mi around Phoenix. Initial model selected to represent long-term trends and weather variables (e.g., ave. daily temp., max daily temp., daily mean specific humidity, etc.); then PM variables added to model one at a time to ascertain which had strongest effect. Piecewise linear analysis and spline analysis used to evaluate possible nonlinear PM-mortality relationship and to evaluate threshold possibilities. Data analyzed most likely same as Clyde's or Mar's Phoenix data.	In linear PM effect model, a statistically significant mortality association found with $PM_{10\text{-}2.5}$, but not with $PM_{2.5}$. In the model allowing for a threshold, evidence suggestive of possible threshold for $PM_{2.5}$ (in the range of 20-25 $\mu g/m^3$) found, but not for $PM_{10\text{-}2.5}$. A seasonal interaction in the $PM_{10\text{-}2.5}$ effect was also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10\text{-}2.5}$ is lowest.	—
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983. PM_{15}: 55.5, 47.0, 47.5; and $PM_{2.5}$: 42.1, 37.1, 39.9, for Newark, Elizabeth, and Camden, respectively.	Factor analysis-derived source type components were examined for their associations with mortality in this study. Non-accidental total deaths and cardiorespiratory deaths were examined for their associations with PM_{15}, $PM_{2.5}$ sulfate, trace metals from PM_{15}, three fractions of extractable organic matter, and CO. Data were analyzed with Poisson GEE regression models with autoregressive correlation structure, adjusting for temperature, time-of-week, and season indicator variables. Individual pollution lag days from 0 to 3, as well as the average concentrations of current and preceding 3 days were considered. Factor analysis of the trace elements, sulfate, and CO data was conducted, and mortality series were regressed on these factor scores.	Factor analysis identified several source types with tracer elements. In Newark, oil burning factor, industrial source factor, and sulfate factor were positively associated with total mortality; and sulfate was associated with cardio-respiratory mortality. In Camden, oil burning and motor vehicle factors were positively associated with total mortality; and, oil burning, motor vehicles, and sulfate were associated with cardio-respiratory mortality. In Elizabeth, resuspended dust was not associated with total mortality; and industrial source (traced by Cd) showed positive associations with cardio-respiratory mortality. On the mass basis (source-contributed mass), the RRs estimates per 10 $\mu g/m^3$ were larger for specific sources (e.g., oil burning, industry, etc.) than for total mass. The choice of lag/averaging reported to be not important.	Percent excess deaths per 50 $\mu g/m^3$ increase in current day PM_{15}: in Newark, 5.7 (4.6, 6.7) for total mortality; in Camden, 7.8 (3.6, 12.1) for cardioresp. mortality; in Camden, 11.1 (0.7, 22.5) and 15.0 (4.3, 26.9); and in Elizabeth, −4.9 (−17.9, 10.9) and 3.0 (−11.0, 19.4), respectively. Percent excess deaths per 25 $\mu g/m^3$ $PM_{2.5}$; in Newark, 4.3 (2.8, 5.9) for total and 5.1 (3.1, 7.2) for cardiorespiratory mortality; in Camden, 5.7 (0.1, 11.5) and 6.2 (0.6, 12.1); in Elizabeth, 1.8 (−5.4, 9.5) and 2.3 (−5.0, 10.1), respectively.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Gamble (1998). Dallas, TX. 1990-1994. PM_{10} (25)	Relationships of total, respiratory, cardiovascular, cancer, and remaining non-accidental deaths to PM_{10}, O_3, NO_2, SO_2, and CO evaluated, adjusting for temperature, dewpoint, day-of-week, and seasonal cycles (trigonometric terms) using Poisson regression.	O_3 (avg. of 1-2 day lags), NO_2 (avg.. 4 -5 day lags), and CO (avg. of lags 5- 6 days) were significantly positively associated with total mortality. PM_{10} and SO_2 were not significantly associated with any deaths.	-3.6% (-12.7, 6.6) per 50 $\mu g/m^3$ PM_{10} at 0 lag (other lags also reported to have no associations)
Ostro (1995). San Bernardino and Riverside Counties, CA, 1980-1986. $PM_{2.5}$ (estimated from visual range). Mean = 32.5.	Study evaluated total, respiratory, cardiovascular, and age > = 65 deaths (mean = 40.7, 3.8, 18.7, and 36.4 per day, respectively). $PM_{2.5}$ estimated based on airport visual range and previously published empirical formula. Autoregressive OLS (for total) and Poisson (for sub-categories) regressions used, adjusting for season (sine/cosine with cycles from 1 yr to 0.75 mo; prefiltering with 15-day moving ave.; dichotomous variables for each year and month; smooth function of day and temp.), day-of-week, temp. and dewpoint. Evaluated lags 0, 1, and 2 of estimated $PM_{2.5}$, as well as moving averages of 2, 3, and 4 days and O_3.	The results were dependent on season. No $PM_{2.5}$ – mortality association found for the full year-round period. Associations between estimated $PM_{2.5}$ (same-day) and total and respiratory deaths found during summer quarters (April - Sept.). Correlation between the estimated $PM_{2.5}$ and daily max temp. was low (r = 0.08) during the summer quarters. Ozone was also associated with mortality, but was also relatively highly correlated with temp. r = 0.73). Moving averages of $PM_{2.5}$ did not improve the associations.	Percent excess deaths per 25 $\mu g/m3$ of estimated $PM_{2.5}$, lag 0: Full year: 0.3 (-0.6, 1.2) for total; 2.1 (-0.3, 4.5) for respiratory; and 0.7 (-0.3, 1.7) for circulatory. Summer quarters: 1.6 (0.03, 3.2) for total; 5.5 (1.1, 10.0) for respiratory; and 0 (-1.0, 1.0) for circulatory.
Kelsall et al. (1997). Philadelphia, PA 1974-1988. TSP (67)	Total, cardiovascular, respiratory, and by-age mortality regressed on TSP, SO_2, NO_2, O_3, and CO, adjusting for temporal trends and weather, using Poisson GAM model.	TSP, SO_2, O_3, and 1-day lagged CO individually showed statistically significant associations with total mortality. No NO_2 associations unless SO_2 or TSP was also considered. The effects of TSP and SO_2 were diminished when both pollutants were included.	Total mortality excess risk: 3.2% (0, 6.1) per 100 $\mu g/m^3$ TSP at 0 day lag.
Moolgavkar and Luebeck (1996). Philadelphia, PA. 1973-1988. TSP (68)	A critical review paper, with an analysis of total daily mortality for its association with TSP, SO_2, NO_2, and O_3, adjusting for temporal trends, temperature, and also conducting analysis by season, using Poisson GAM model.	RR results presented as figures, and seasonal difference noted. TSP, SO_2, O_3 - mortality associations varied across season. TSP associations were stronger in summer and fall. NO_2 was the most significant predictor.	Total mortality excess risk: ranged $\approx$ 0 (winter) to $\approx$4% (summer) per 100 $\mu g/m^3$ TSP at 1 day lag.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Neas et. al. (1999). Philadelphia. 1973-1980. TSP mean = 77.2.	Total, age over 65, cancer, and cardiovascular deaths analyzed for association with TSP. Conditional logistic regression analysis with case-crossover design conducted. Average values of current and previous days' TSP used. Case period is the 48-hr period ending at midnight on day of death. Control periods are 7, 14, and 21 days before and after the case period. Other covariates included temperature on the previous day, dewpoint on the same day, an indicator for hot days (> 80°F), an indicator for humid days (dewpoint > 66°F), and interaction of same-day temp. and winter season.	In each set of the six control periods, TSP was associated with total mortality. A model with four symmetric reference periods 7 and 14 days around the case period produced a similar result. A model with only two symmetric reference periods of 7 days around the case produced a larger estimate. A larger effect was seen for deaths in persons $\geq$ 65 years of age and for deaths due to pneumonia and to cardiovascular disease. Cancer mortality was not associated with TSP.	Odds Ratio (OR) for all cause mortality per 100 $\mu g/m^3$ increase in 48-hr mean TSP was 1.056 (1.027, 1.086). The corresponding number for those aged 65 and over was 1.074 (1.037, 1.111), and 1.063 (1.021, 1.107) for cardiovascular disease.
Schwartz (2000d). Philadelphia. 1974-1988. TSP. Mean = 70 $\mu g/m^3$ for warm season (April through August) and 64 $\mu g/m^3$ for cold season.	Total (non-accidental) deaths analyzed. GAM Poisson models adjusting for temperature, dewpoint, day-of-week, and season applied to each of 15 warm and cold seasons. Humidity-corrected extinction coefficient, derived from airport visual range, also considered as explanatory variable. In the second stage, resulting 30 coefficients were regressed on regression coefficients of TSP on SO$_2$. Results of first stage analysis combined using inverse variance weighting.	When TSP controlled for, no significant association between SO$_2$ and daily deaths. SO$_2$ had no association with daily mortality when it was poorly correlated with TSP. In contrast, when SO$_2$ was controlled for, TSP was more strongly associated with mortality than when it was less correlated with SO$_2$. However, all of the association between TSP and mortality was explained by its correlation with extinction coefficient.	Total mortality excess risk estimates combined across seasons/years: 9.0 (5.7, 12.5) per 100 $\mu g/m^3$ TSP.
Levy et al. (2000). Years vary from study to study ranging between 1973 to 1994. 21 published studies included U.S., Canadian, Mexican, European, Australian, and Chilean cities. PM$_{10}$ levels in the 19 U.S. cities (in some cases TSP were converted to PM$_{10}$ using factor of 0.55) ranged from ~20 to ~60 ug/m^3.	To determine whether across-study heterogeneity of PM effects could be explained by regional parameters, Levy et al. applied an empirical Bayes meta-analysis to 29 PM estimates from 21 published studies. They considered such city-specific variables as mortality rate, gaseous pollutantsπ regression coefficients, PM$_{10}$ levels, central air conditioning prevalence, heating and cooling degree days.	Among the city-specific variables, PM$_{2.5}$/PM$_{10}$ ratio was a significant predictor (larger PM estimates for higher PM$_{2.5}$/PM$_{10}$ ratios) in the 19 U.S. cities data subsets. While the sulfate data were not available for all the 19 cities, the investigators noted that, based on their analysis of the limited data with sulfate for 10 estimates, the sulfate/PM10 ratio was highly correlated with both the mortality (r = 0.84) and with the PM$_{2.5}$/PM$_{10}$ ratio (r = 0.70). This indicates that the sulfate/PM$_{10}$ ratio may be even better predictor of regional heterogeneity of PM RR estimates.	The pooled estimate from 19 U.S. cities was 0.70% (0.54, 0.84) per 10 ug/m3 increase in PM$_{10}$.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada			
Burnett et al. (1998a). 11 Canadian cities. 1980-1991. No PM index data available on consistent daily basis.	Total non-accidental deaths were linked to gaseous air pollutants (NO_2, O_3, SO_2, and CO) using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather (selected from spline-smoothed functions of temperature, dewpoint, relative humidity with 0, 1, and 2 day lags using forward stepwise procedure). Pollution variables evaluated at 0, 1, 2, and up to 3-day lag averages thereof. No PM index included in analyses because daily PM measurements not available. City-specific models containing all four gaseous pollutants examined. Overall risks computed by averaging risks across cities.	NO_2 had 4.1% increased risk per mean concentration; O_3 had 1.8%; SO_2 had 1.4%, and CO had 0.9% in multiple pollutant regression models. A 0.4% reduction in excess mortality was attributed to achieving a sulfur content of gasoline of 30 ppm in five Canadian cities. Daily PM data for fine and coarse mass and sulfates available on varying (not daily) schedules allowed ecologic comparison of gaseous pollutant risks by mean fine particle indicators mass concentrations.	Found suggestion of weak negative confounding of NO_2 and SO_2 effects with fine particles and weak positive confounding of particle effects with O_3. No quantitative RR or ER estimates reported for PM indicators.
Burnett et al. (2000). 8 largest Canadian cities. 1986-1996. All city mean PM_{10} 25.9; $PM_{2.5}$ 13.3; $PM_{10-2.5}$ 12.6; sulfate 2.6.	Total non-accidental deaths linked to PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO). Each city's mortality, pollution, and weather variables separately filtered for seasonal trends and day-of-week patterns. The residual series from all the cities then analyzed in a GAM Poisson model. The weather model was selected from spline-smoothed functions of temperature, relative humidity, and maximum change in barometric pressure within a day, with 0 and 1 day lags using forward stepwise procedure. Pollution effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-pollutant models, principal components were also used as predictors in the regression models.	O_3 was weakly correlated with other pollutants and other pollutants were "moderately" correlated with each other (the highest was r = 0.65 for NO_2 and CO). The strongest association with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger predictor of mortality than $PM_{10-2.5}$. The estimated gaseous pollutant effects were generally reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10-2.5}$. Sulfate, Fe, Ni, and Zn were most strongly associated with mortality. Total effect of these four components was greater than that for $PM_{2.5}$ mass alone.	Percentage increase in daily filtered non-accidental deaths associated with increases of 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ at lag 1 day: 3.5 (1.0, 6.0) for PM_{10}; 3.0 (1.1, 5.0) for $PM_{2.5}$; and 1.8 (−0.7, 4.4) for $PM_{10-2.5}$. In the multiple pollutant model with $PM_{2.5}$, $PM_{10-2.5}$, and the 4 gaseous pollutants, 1.9 (0.6, 3.2) for $PM_{2.5}$; and 1.2 (−1.3, 3.8) for $PM_{10-2.5}$.
Burnett et al. (1998b). Toronto, 1980-1994. TSP (60); COH (0.42); SO4= (9.2 $\mu g/m^3$); PM_{10} (30, estimated); $PM_{2.5}$ (18, estimated)	Total, cardiac, and other nonaccidental deaths (and by age groups) were regressed on TSP, COH, SO_4=, CO, NO_2, SO_2, O_3, estimated PM_{10} and $PM_{2.5}$ (based on the relationship between the existing every-6th-day data and SO_4=, TSP and COH), adjusting for seasonal cycles, day-of-week, temperature, and dewpoint using Poisson GAM model.	Essentially all pollutants were significant predictors of total deaths in single pollutant models, but in two pollutant models with CO, most pollutants' estimated RRs reduced (all PM indices remained significant). Based on results from the co-pollutant models and various stepwise regressions, authors noted that effects of the complex mixture of air pollutants could be almost completely explained by the levels of CO and TSP.	Total mortality percent excess: 2.3% (0.8, 3.8) per 100 $\mu g/m^3$ TSP; 3.5% (1..8, 5.3) per 50 $\mu g/m^3$ PM_{10}; 4.8% (3.3, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$. 0 day lag for TSP and PM_{10}; Avg. of 0 and 1 day for $PM_{2.5}$.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Goldberg et al. (2000) Montreal, Quebec 1984-95 Mean TSP = 53.1 (14.6 - 211.1) $\mu g/m^3$ PM$_{10}$ = 32.2 (6.5 - 120.5) $\mu g/m^3$ PM$_{2.5}$ = 3.3 (0.0 - 30.0) $\mu g/m^3$	Study aimed to shed light on population subgroups that my be susceptible to PM effects. Linked data on daily deaths with other health data (physician visits, pharmaceutical R$_x$, etc.) to identify individuals with presenting health conditions. PM$_{10}$ and PM$_{2.5}$ measured by dichotomous sampler 1 in 6 days until 1992 (2 stations), then daily through 1993. PM missing days interpolated from COH, ext. coefficient, sulfates. Used quasi likelihood estimation in GAM's to assess PM associations with total and cause-specific mortality; and, also, in subgroups by age and/or preexisting health conditions. Adjusted for CO, NO$_2$, NO, O$_3$ and SO$_2$ in 2-pollutant and all-pollutant models.	Significant associations found for all-cause (total non-accidental) and cause-specific (cancer, CAD, respiratory disease, diabetes) with PM measures. Results reported for PM$_{2.5}$, COH and sulfates. All three PM measures associated with increases in total, resp., and "other nonaccidental", and diabetes-related mortality. No PM associations found with digestive, accidental, renal or neurologic causes of death. Also, mainly in 65+ yr group, found consistent associations with increased total mortality among persons who had cancer, acute lower resp. diseases, any cardiovascular disease, chronic CAD and congestive heart failure (CHF).	Percent excess mortality per 25 $\mu g/m^3$ estimated PM$_{2.5}$: Total deaths (3 d ave.) = 4.4% (2.5, 6.3) CV deaths (3 d ave.) = 2.6% (−0.1, 5.5) Resp deaths (3 d ave.) = 16.0% (9.7, 22.8) Coronary artery (3 d ave.) = 3.4% (−0.2, 7.1) Diabetes (3 d ave.) = 15.7% (4.8, 27.9) Lower Resp Disease (3 d ave.) = 9.7% (4.5, 15.1) Airways disease (3 d ave.) = 2.7% (−0.9, 6.4) CHF (3 d ave.) = 8.2% (3.3, 13.4)
Goldberg et al. (2001). Montreal, Quebec. 1984-1993. Predicted PM$_{2.5}$ mean = 17.6. CoH (1000ft)) mean = 0.24, sulfate mean =3.3.	The investigators used the universal Quebec medicare system to obtain disease conditions prior to deaths, and the roles of these respiratory and cardiovascular conditions in the PM-mortality associations were examined. GAM Poisson model adjusting for temporal pattern and weather was used.	The PM-mortality associations were found for those who had acute lower respiratory diseases, chronic coronary diseases, and congestive heart failure. They did not find PM-mortality associations for those chronic upper respiratory diseases, airways disease, cerebrovascular diseases, acute coronary artery diseases, and hypertension. Adjusting for gaseous pollutants generally attenuated PM RR estimates, but the general pattern remained. Effects were larger in summer.	The percent excess deaths estimates for non-accidental deaths per IQR (average of 0-2 day lags) for CoH, predicted PM$_{2.5}$, and sulfate were: 1.98% (1.07, 2.90), 2.17% (1.26, 3.08), and 1.29% (0.68, 1.90), respectively.
Goldberg et al. (2001). Data same as above.	Cause-specific mortality (non-accidental, neoplasm, lung cancer, cardiovascular, coronary artery disease, diabetes, renal disease, and respiratory) series were examined for their associations with O$_3$, using GAM Poisson model adjusting for temporal pattern and weather. Results were also reported for models with adjustments for other pollutants (SO$_2$, CO, NO$_2$, CoH, etc.).	The effect of O$_3$ was generally higher in the warm season and among persons aged 65 years and over. O$_3$ showed positive and statistically significant associations with non-accidental cause, neoplasms, cardiovascular disease, and coronary artery disease. These associations were not reduced when the model adjusted for SO$_2$, CO, NO$_2$, CoH. simultaneously (or when CoH was replaced with PM$_{2.5}$ or total sulfates).	PM RRs not reported.
Özkaynak et al. (1996). Toronto, 1970-1991. TSP (80); COH (0.42 /1000ft).	Total, cardiovascular, COPD, pneumonia, respiratory, cancer, and the remaining mortality series were related to TSP, SO$_2$, COH, NO$_2$, O$_3$, and CO, adjusting for seasonal cycles (by high-pass filtering each series) temperature, humidity, day-of-week, using OLS regression. Factor analysis of multiple pollutants was also conducted to extract automobile related pollution, and mortality series were regressed on the resulting automobile factor scores.	TSP (0 day lag) was significantly associated with total and cardiovascular deaths. NO$_2$ (0-day lag) was a significant predictor for respiratory and COPD deaths. 2-day lagged O$_3$ was associated with total, respiratory, and pneumonia deaths. Factor analysis showed factor with high loadings for NO$_2$, COH, and CO (apparently representing automobile factor) as significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.	Total mortality excess risk: 2.8% per 100 $\mu g/m^3$ TSP at 0 day lag.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Katsouyanni et al. (1997). 12 European (APHEA) cities. 1975-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Athens and Kracow.	Total daily deaths regressed on BS or SO_2 using Poisson models, adjusting for seasonal cycles, day-of-week, influenza epidemic, holidays, temp., humidity. Final analysis done with autoregressive Poisson models to allow for overdispersion and autocorrelation. Pollution effects examined at 0 through 3 day lags and multi-day averages thereof. When city-specific coefficients tested to be homogeneous, overall estimates obtained by computing variance-weighted means of city-specific estimates (fixed effects model). When significant heterogeneity present, source of heterogeneity sought by examining a predefined list of city-specific variables, including annual and seasonal means of pollution and weather variables, number of monitoring sites, correlation between measurements from different sites, age-standardized mortality, proportion of elderly people, smoking prevalence, and geographic difference (north-south, east-west). A random effects model was fit when heterogeneity could not be explained.	Substantial variation in pollution levels (winter mean SO_2 ranged from 30 to 330 $\mu g/m^3$), climate, and seasonal patterns were observed across cities. Significant heterogeneity was found for the effects of BS and SO_2, but only the separation between western and central eastern European cities resulted in more homogeneous subgroups. Significant heterogeneity for SO_2 remained in western cities. Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both SO_2 and BS were stronger during the summer and were independent.	Total mortality excess deaths per 25 $\mu g/m^3$ increase in single day BS for western European cities: 1.4 (1.0, 1.8); and 2 (1, 3) per 50 $\mu g/m^3$ PM_{10} increase. In central/eastern Europe cities, corresponding figure was 0.3 (0.05, 0.5) per 25 $\mu g/m^3$ BS.
Samoli et al. (2001). APHEA 1 cities (see Katsouyanni (1997)). At least five years between 1980-1992. The PM levels are the same as those in Katsouyanni et al. (1997).	In order to further investigate the source of the regional heterogeneity of PM effects, and to examine the sensitivity of the RRs, the APHEA data were reanalyzed by the APHEA investigators themselves (Samoli et al., 2001). Unlike previous model in which sinusoidal terms for seasonal control and polynomial terms for weather, the investigators this time used a GAM model with smoothing terms for seasonal trend and weather, which is more commonly used approach in recent years.	T he estimated relative risks for central-eastern cities were larger than those obtained from the previous model. Also, restricting the analysis to days with concentration < 150ug/m3 further reduced the differences between the western and central-eastern European cities. The authors concluded that part of the heterogeneity in the estimated air pollution effects between western and central eastern cities in previous publications was caused by the statistical approach and the data range.	Total mortality RRs per 50ug/m3 BS for all cities, western cities, and central-eastern cities using the GAM approach were: 2.2% (1.8, 2.6); 3.1% (2.4, 3.9); and, 2.2% (1.4, 2.3), respectively. In contrast, those with old method were: 1.3% (0.9, 1.7); 2.9% (2.1, 3.7); and, 0.6% (0.1, 1.1), respectively.
Katsouyanni et al. (2001). 1990-1997 (variable from city to city). Median PM_{10} ranged from 14 (Stockholm) to 66 (Prague). Median BS ranged from 10 (Dublin) to 64 (Athens).	The 2nd phase of APHEA (APHEA 2) put emphasis on the effect modification by city-specific factors. The first stage of city specific regressions used GAM Poisson model. The second stage regression analysis was conducted to explain any heterogeneity of air pollution effects using city-specific variables. These city-specific variables included average air pollution levels, average temperature/humidity, age-standardize mortality rate, region indicators, etc.	The authors found several effect modifiers. The cities with higher NO_2 levels showed larger PM effects. The cities with warmer climate showed larger PM effects. The cities with low standardized mortality rate showed larger PM effects. The combined estimate of mortality RRs per 10ug/m3 PM_{10} or BS was: 0.6% (0.4, 0.8). The PM RR estimates for cities with low vs. high NO2 levels were 0.19% (0, 0.41) and 0.80% (0.67, 0.93); 0.29% (0.16, 0.42) for cities with cold climate and 0.82% (0.69, 0.96) for warm climate, respectively.	
Touloumi et al. (1997). 6 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 14.6 in London to 84.4 in Athens.	Results of the short-term effects of ambient NO_2 and/or O_3 on daily deaths from all causes (excluding accidents) were discussed to provide a basis for comparison with estimated SO_2 or BS effects in APHEA cities. Poisson models, lag/averaging of pollution, and the computation of combined effects across the cities were done in the same way as done by Katsouyanni et al. (1997), as above.	Significant positive associations found between daily deaths and both NO_2 and O_3. Tendency for larger effects of NO_2 in cities with higher levels of BS. When BS included in the model, pooled estimate for O_3 effect only slightly reduced, but coefficient for NO_2 reduced by half. Authors speculated that short-term effects of NO_2 on mortality confounded by other vehicle-derived pollutants.	NO_2 and/or O_3 estimates only.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Zmirou et al. (1998). 10 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Kracow.	Cardiovascular, respiratory, and digestive mortality series in 10 European cities analyzed to examine cause-specificity of air pollution. The mortality series were analyzed for associations with PM (BS, except TSP in Milan and Bratislava; PM_{13} in Lyon), NO_2, O_3, and SO_2. Poisson models, lag/averaging of pollution, and computation of combined effects across the cities done in the same way as by Katsouyanni et al. (1997), above.	The cardiovascular and respiratory mortality series were associated with BS and SO_2 in western European cities, but not in the five central European cities. NO_2 did not show consistent mortality associations. RRs for respiratory causes were at least equal to, or greater than those for cardiovascular causes. No pollutant exhibited any association with digestive mortality.	Pooled cardiovascular mortality percent excess deaths per 25 $\mu g/m^3$ increase in BS for western European cities: 1.0 (0.3, 1.7); for respiratory mortality, it was 2.0 (0.8, 3.2) in single lag day models (the lags apparently varied across cities).
Bremner et al. (1999). London, UK, 1992-1994. BS (13), PM_{10} (29).	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tend to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	1.9% (0.0, 3.8) per 25 $\mu g/m^3$ BS at lag 1 day; 1.3% (-1.0, 3.6) per 50 $\mu g/m^3$ PM_{10} at lag 1 d for total deaths. Resp. deaths (3 d) = 4.9% (0.5, 9.4). CVD deaths (1 d) = 3.0% (0.3, 5.7).
Prescott et al. (1998). Edinburgh, UK, 1981-1995. PM_{10} (21, by TEOM only for 1992-1995); BS (8.7).	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and >= 65), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	3.8 (1.3, 6.4) per 25 $\mu g/m^3$ increase in BS for all cause mortality in age 65+ group, avg. of 1-3 day lags.
Rooney et al. (1998). England and Wales, and Greater London, UK PM_{10} (56, during the worst heat wave; 39, July-August mean)	Excess deaths, by age, sex, and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-94 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987-1992 study (Anderson et al., 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave.
Wordley et al. (1997). Birmingham, UK, 1992-1994. PM_{10} (apparently beta-attenuation, 26)	Mortality data were analyzed for COPD, pneumonia, all respiratory diseases, all circulatory diseases, and all causes. Mortality associations with PM_{10}, NO_2, SO_2, and O_3 were examined using OLS (with some health outcomes log- or square-root transformed), adjusting for day-of-week, month, linear trend, temperature and relative humidity. The study also analyzed hospital admission data.	Total, circulatory, and COPD deaths were significantly associated with 1-day lag PM_{10}. The gaseous pollutants "did not have significant associations independent from that of PM_{10}", and the results for gaseous pollutants were not presented. The impact of reducing PM_{10} to below 70 $\mu g/m^3$ was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70 $\mu g/m^3$ occurred only once during the study period.	5.6% (0.5, 11.0) per 50 $\mu g/m^3$ PM_{10} at 1 d lag for total deaths. COPD (1 d lag) deaths = 27.6 (5.1, 54.9). Circulatory (1 d) deaths = 8.8 (1.9, 17.1)

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (2000). The Netherlands, 1986-1994. PM_{10} (median 34); BS (median 10).	Total, cardiovascular, COPD, and pneumonia mortality series were regressed on PM_{10}, BS, sulfate, nitrate, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model. Deaths occurring inside and outside hospitals were also examined.	Particulate air pollution was not more consistently associated with mortality than were the gaseous pollutants SO_2 and NO_2. Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}. The RRs for all pollutants were larger in the summer months than in the winter months.	0.9 (0.1, 1.7) per 50 $\mu g/m^3$ PM_{10}; 1.0 (0.5, 1.5) per 25 $\mu g/m^3$ BS; 3.2 (0.6, 5.9) per 25 $\mu g/m^3$ sulfate; and 4.1 (1.4, 6.9) per 25 $\mu g/m^3$ nitrate, all at 1 day lag.
Hoek et al. (2001). The Netherlands. 1986-1994. PM10 (median 34); BS (median 10).	This study of the whole population of the Netherlands, with its large sample size (mean daily total deaths ~ 330, allowed examination of specific cardiovascular cause of deaths. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week was used.	Deaths due to heart failure, arrhythmia, cerebrovascular causes, and thrombocytic causes were more strongly (~ 2.5 to 4 times larger relative risks) associated with air pollution than the overall cardiovascular deaths (CVD) or myocardial infarction (MI) and other ischemic heart disease (IHD).	For PM_{10} (7-day mean), RRs for total CVD, MI/IHD, arrhythmia, heart failure, cerebrovascular, and thrombocytic mortality per 80 ug/m3 increase were: 1.2% (-1.6, 4.1), 0.5% (-3.6, 4.8), 4.1% (-6.8, 16.3), 3.6% (-4.0, 11.8), 3.1% (-2.9, 9.4), and 1.0% (-10.6, 14.3), respectively. The RRs for BS were larger and more significant than those for PM_{10}.
Pönkä et al. (1998). Helsinki, Finland, 1987-1993. TSP (median 64); PM_{10} (median 28)	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant significantly associated with mortality from all cardiovascular or CVD causes in 65+ year age group. Only in age <65 year group, PM_{10} associated with total and CVD deaths with 4 and 5 d lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with CVD mortality <65 yr. group with inconsistent signs and late and spiky lags (neg. on d 5 and pos. on d 6).	18.8% (5.6, 33.2) per 50 $\mu g/m^3$ PM_{10} 4 day lag (other lags negative or zero).
Peters et al. (1999a). A highly polluted coal basin area in the Czech Republic and a rural area in Germany, northeast Bavaria districts. 1982-1994. TSP: mean = 121.1 and 51.6, respectively, for these two regions. PM_{10} and $PM_{2.5}$ were also measured in the coal basin during 1993-1994 (mean = 65.9 and 51.0, respectively).	Non-accidental total and cardiovascular deaths (mean = 18.2 and 12.0 per day, for the Czech and Bavaria areas, respectively). The APHEA approach (Poisson model with sine/cosine, temperature as a quadratic function, relative humidity, influenza, day-of-week as covariates), as well as GAM Poisson models were considered. Logarithm of TSP, SO_2, NO_2, O_3, and CO (and PM_{10} and $PM_{2.5}$ for 1993-1994) were examined at lags 0 through 3 days.	In the coal basin (i.e., the Czech Republic polluted area), on the average, 68% of the TSP was PM_{10}, and most of PM_{10} was $PM_{2.5}$ (75%). For the coal basin, associations were found between the logarithm of TSP and all-cause mortality at lag 1 or 2 days. SO_2 was also associated with all-cause mortality with slightly lower significance. PM_{10} and $PM_{2.5}$ were both associated with all-cause mortality in 1993-1994 with a lag of 1-day. NO_2, O_3, and CO were positively but more weakly associated with mortality than PM indices or SO_2. In the Bavarian region, neither TSP nor SO_2 was associated with mortality, but CO (at lag 1-day) and O_3 (at lag 0-day) were associated with all-cause mortality.	Total mortality excess deaths per 100 $\mu g/m^3$ increase in TSP for the Czech region: 3.8 (0.8, 6.9) at lag 2-day for 1982-1994 period. For period 1993-1994, 9.5 (1.2, 18.5) per 100 $\mu g/m^3$ increase in TSP at lag 1-day, and 4.8 (0.7, 9.0) per 50 $\mu g/m^3$ increase in PM_{10}; and 1.4 (−0.5, 3.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (1997). Rotterdam, the Netherlands, 1983-1991. TSP (median 42); BS (median 13).	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	5.5 (1.1, 9.9) per 100 $\mu g/m^3$ TSP at 1 day lag.
Kotěšovec et al. (2000). Northern Bohemia, Czech Republic, 1982-1994. TSP (121.3).	Total (excluding accidents and children younger than 1 yr), cause specific (cardiovascular and cancer), age (65 and less vs. otherwise), and gender specific mortality series were examined for their associations with TSP and SO_2 using logistic model, adjusting for seasonal cycles, influenza epidemics, linear and quadratic temperature terms. Lags 0 through 6 days, as well as a 7 day mean values were examined.	For the total mortality, TSP, but not SO_2, was associated. There were apparent differences in associations were found between men and women. For example, for age below 65 cardiovascular mortality was associated with TSP for men but not for women.	Total mortality percent excess deaths per 100 $\mu g/m^3$ increase in TSP at 2 day lag was 3.4 (0.5, 6.4).
Zanobetti et al. (2000a). Milan, Italy. 1980-1989. TSP mean = 142.	The focus of this study was to quantify mortality displacement using GAM distributed lag models. Non-accidental total deaths were regressed on smooth function of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect.	TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.	Total mortality percent increase estimates per IQR increase in TSP: 2.2 (1.4, 3.1) for single-day model; 6.7 (3.8, 9.6) for distributed lag model.
Anderson et al. (1996). London, UK, 1987-1992. BS (15)	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	Both O_3 (0 day lag) and BS (1 day lag) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	2.8% (1.4, 4.3) per 25 $\mu g/m^3$ BS at 1-d lag for total deaths. CVD (1 d) = 1.0 (-1.1, 3.1). Resp. (1 d) = 1.1 (-2.7, 5.0).

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Michelozzi et al. (1998). Rome, Italy, 1992-1995. TSP ("PM_{13}" beta attenuation, 84).	Total mortality was related to PM_{13}, SO_2, NO_2, CO, and O_3, using Poisson GAM model , adjusting for seasonal cycles, temperature, humidity, day-of-week, and holiday. Analysis of mortality by place of residence, by season, age, place of death (in or out of hospital), and cause was also conducted.	PM_{13} and NO_2 were most consistently associated with mortality. CO and O_3 coefficients were positive, SO_2 coefficients negative. RR estimates higher in the warmer season. RRs similar for in- and out-of hospital deaths.	1.9% (0.5, 3.4) per 50 $\mu g/m^3$ PM_{13} at 0 day lag.
Garcia-Aymerich et al. (2000). Barcelona, Spain. 1985-1989. Black Smoke no data distribution was reported).	Daily total (mean = 1.8/day), respiratory, and cardiovascular mortality counts of a cohort (9,987 people) with COPD or asthma were associated with black smoke (24-hr), SO_2 (24-hr and 1-hr max), NO_2 (24-hr and 1-hr max), O_3 (1-hr max), temperature, and relative humidity. Poisson regression models using APHEA protocol were used. The resulting RRs were compared with those of the general population.	Daily mortality in COPD patients was associated with all six pollution indices. This association was stronger than in the general population only for daily 1-hr max of SO_2, daily 1-hr max and daily means of NO_2. BS and daily means of SO_2 showed similar or weaker associations for COPD patients than for the general population.	Total mortality percent increase per 25 $\mu g/m^3$ increase in avg. of 0-3 day lags of BS: 2.76 (1.31, 4.23) in general population, and 1.14 (−4.4, 6.98) in the COPD cohort.
Rahlenbeck and Kahl (1996). East Berlin, 1981-1989. "SP" (beta attenuation, 97)	Total mortality (as well as deviations from long-wave cycles) was regressed on SP and SO_2, adjusting for day-of-week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 $\mu g/m^3$.	Both SP and SO_2 were significantly associated with total mortality with 2 day lag in single pollutant model. When both pollutants were included, their coefficients were reduced by 33% and 46% for SP and SO_2, respectively.	6.1% per 100 $\mu g/m^3$ "SP" at 2 day lag.
Rossi et al. (1999). Milan, Italy, 1980-1989 TSP ("PM_{13}" beta attenuation, 142)	Specific causes of death (respiratory, respiratory infections, COPD, circulatory, cardiac, heart failure, and myocardial infarction) were related to TSP, SO_2, and NO_2, adjusting for seasonal cycles, temperature, and humidity, using Poisson GAM model.	All three pollutants were associated with all cause mortality. Cause-specific analysis was conducted for TSP only. Respiratory infection and heart failure deaths were both associated with TSP on the concurrent day, whereas the associations for myocardial infarction and COPD deaths were found for the average of 3 to 4 day prior TSP.	3.3% (2.4, 4.3) per 100 $\mu g/m^3$ TSP at 0 day lag.
Sunyer et al. (2000). Barcelona, Spain. 1990-1995. BS means: 43.9 for case period, and 43.1 for control period.	Those over age 35 who sought emergency room services for COPD exacerbation during 1985-1989 and died during 1990-1995 were included in analysis. Total, respiratory, and cardiovascular deaths were analyzed using a conditional logistic regression analysis with a case-crossover design, adjusting for temperature, relative humidity, and influenza epidemics. Bi-directional control period at 7 days was used. Average of the same and previous 2 days used for pollution exposure period. Data also stratified by potential effect modifiers (e.g., age, gender, severity and number of ER visits, etc.).	BS levels were associated with all cause deaths. The association was stronger for respiratory causes. Older women, patients admitted to intensive care units, and patients with a higher rate of ER visits were at greater risk of deaths associated with BS.	Percent increase per 25 $\mu g/m^3$ increase in 3-day average BS: 14.2 (1.6, 28.4) for all causes; 9.7 (−10.2, 34.1) for cardiovascular deaths; 23.2 (3.0, 47.4) for respiratory deaths.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Sunyer and Basagana (2001). Barcelona, Spain. 1990-1995. See Sunyer et al. (2000) for PM levels.	The analysis assessed any "independent" particle effects, after controlling for gaseous pollutants, on a cohort of patients with COPD (see the summary description for Sunyer et al. (2000) for analytical approach). PM_{10}, NO_2, O_3, and CO were analyzed.	PM_{10}, but not gaseous pollutants were associated with mortality for all causes. In the two-pollutant models, the PM_{10}-mortality associations were not diminished, whereas those with gaseous pollutants were.	Odds ratio for all cause mortality per IQR PM_{10} on the same-day (27 ug/m3) was 11% (0, 24). In two pollutant models, the PM_{10} RRs were 10.5%, 12.9%, and 10.8% with NO_2, O_3, and CO, respectively.
Tobias and Campbell (1999). Barcelona, Spain. 1991-1995. Black Smoke (BS) (no data distribution was reported).	Study examined the sensitivity of estimated total mortality effects of BS to different approaches to modeling influenza epidemics: (1) with a single dummy variable; (2) with three dummy variables; (3) using daily number of cases of influenza. Poisson regression used to model total daily mortality, adjusting for weather, long-term trend, and season, apparently following APHEA protocol.	Using the reported daily number of influenza cases resulted in a better fit (i.e., a lower AIC) than those using dummy variables. In the "better" model, the black smoke coefficient was about 10% smaller than those in the models with dummy influenza variables, but remained significant. Lags not reported.	Total mortality excess deaths per 25 $\mu g/m^3$ increase in BS: 1.37 (0.20, 2.56) for model using the daily case of influenza; 1.71 (0.53, 2.91) for model with three influenza dummy variables.
Alberdi Odriozola et al. (1998). Madrid, Spain, 1986-1992. "TSP" (beta attenuation, 47 for average of 2 stations)	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (1-day lag) and SO_2 (3-day lagged) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 $\mu g/m^3$ TSP at lag 1 day.
Díaz et al. (1999). Madrid, Spain. 1990-1992. TSP (no data distribution was reported).	Non-accidental, respiratory, and cardiovascular deaths (mean = 62.4, 6.3, and 23.8 per day, respectively). Auto-regressive Integrated Moving Average (ARIMA) models fit to both depend. and independ. variables first to remove auto-correlation and seasonality (i.e., pre-whitening"), followed by examining cross-correlation to find optimal lags. Multivariate OLS models thus included ARIMA components, seasonal cycles (sine/cosine), V-shaped temp., and optimal lags found for pollution and weather variables. TSP, SO_2, NO_2, and O_3 examined. Season-specific analyses also conducted.	TSP was significantly associated with non-accidental mortality at lag 0 for year around and winter, but with a 1-day lag in summer. A similar pattern was seen for circulatory deaths. For respiratory mortality, a significant association with TSP was found only in summer (0-day lag). SO_2, NOx, and NO_2 showed similar associations with non-accidental deaths at lag 0 day. O_3' associations with non-accidental mortality was U-shaped, with inconsistent lags (1, 4, and 10).	For non-accidental mortality, excess deaths was 7.4% (confidence bands not reported; $p < 0.05$) per 100 $\mu g/m^3$ TSP at 0 day lag.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Wichmann et al., (2000). Erfurt, Germany. 1995-1998. Number counts (NC) & mass concentrations (MC) of ultrafine particles in three size classes, 0.01 to 0.1 μm, and fine particles in three size classes from 0.1 to 2.5 μm diameter, using Spectrometryll Mobile Aerosol Spectrometry (MAS). MAS MC $PM_{2.5-0.01}$ (mean 25.8, median 18.8, IQR 19.9). Filter measurements of PM_{10} (mean 38.2, median 31.0, IQR 27.7) and $PM_{2.5}$ (mean 26.3, median 20.2, IQR 18.5). MAS $NC_{2.5-0.01}$ (mean 17,966 per cu.cm, median 14,769, IQR 13,269).	Total non-accidental, cardiovascular, and respiratory deaths (mean 4.88, 2.87, 1.08 per day, respectively) were related to particle mass concentration and number counts in each size class, and to mass concentrations of gaseous co-pollutants NO_2, CO, SO_2, using GAM regression models adjusted for temporal trends, day of week, weekly national influenza rates, temperature and relative humidity. Data analyzed by season, age group, and cause of death separately. Single-day lags and polynomial distributed lag models (PDL) used. Particle indices and pollutants fitted using linear, log-transformed, and LOESS transformations. Two-pollutant models with a particle index and a gaseous pollutant were fitted. The "best" model as used by Wichmann et al. (2000) was that having the highest t-statistic, since other criteria (e.g., log-likelihood for nested models) and AIC for non-nested models could not be applied due to different numbers of observations in each model. There should be little difference between these approaches and resulting differences in results should be small in practice. Sensitivity analyses included stratifying data by season, winter year, age, cause of death, or transformation of the pollution variable (none, logarithmic, non-parametric smooth).	Loss of stat. power by using a small city with a small number of deaths was offset by advantage of having good exposure representation from single monitoring site. Since ultrafine particles can coagulate into larger aggregates in a few hours, ultrafine particle size and numbers can increase into the fine particle category, resulting in some ambiguity. Significant associations were found between mortality and ultrafine particle number concentration (NC), ultrafine particle mass concentration (MC), fine particle mass concentration, or SO_2 concentration. The correlation between $MC_{0.01-2.5}$ and $NC_{0.01-0.1}$ is only moderate, suggesting it may be possible to partially separate effects of ultrafine and fine particles. The most predictive single-day effects are either immediate (lag 0 or 1) or delayed (lag 4 or 5 days), but cumulative effects characterized by PDL are larger than single-day effects. The significance of SO_2 is robust, but hard to explain as a true causal factor since its concentrations are very low. Age is an important modifying factor, with larger effects at ages < 70 than $\geq$ 70 years. Respiratory mortality has a higher RR than cardio- vascular mortality. A large number of models were fitted, with some significant findings of association between mortality and particle mass or number indices.	Total mortality excess deaths: Filter PM_{10} (0-4 d lag) = 6.6 (0.7, 12.8) per 50 $\mu g/m^3$. Filter $PM_{2.5}$ (0-1 d) = 3.0 (−1.7, 7.9). MC for $PM_{0.01-2.5}$ 6.2% (1.4, 11.2) for all year; by season, Winter = 9.2% (3.0, 15.7) Spring = 5.2% (−2.0, 12.8) Summer = −4.7% (−18.7, 11.7) Fall = 9.7% (1.9, 18.1) For ultrafine PM, NC 0.01-0.1 (0-4 d lag): All Year = 8.2% (0.3, 16.9) Winter = 9.7% (0.3, 19.9) Spring = 10.5% (−1.4, 23.9) Summer = −13.9% (−29.8, 5.7) Fall = 12.0% (2.1, 22.7)
Zeghnoun et al. (2001). Rouen and Le Havre, France. 1990-1995. PM_{13} mean = 32.9 for Rouen, 36.4 for Le Havre. BS mean = 18.7 for Rouen, 16.3 for Le Havre.	Total, cardiovascular, and respiratory mortality series were regressed on BS, PM_{13}, SO_2, NO_2, and O_3 in 1- and 2-pollutant models using GAM Poisson models adjusting for seasonal trends, day-of-week, and weather.	In Rouen, O_3, SO_2, and NO_2 were each significantly associated with total, respiratory, and cardiovascular mortality, respectively. In Le Havre, SO_2 and PM_{13} were associated with cardiovascular mortality. However, the lack of statistical significance reported for most of these results may be in part due to the relatively small population size of these cities (430,000 and 260,000, respectively).	PM_{13} total mortality RRs per IQR were 0.5% (-1.1, 2.1) in Rouen (IQR=20.6, 1-day lag) and 1.9% (-0.8, 7.4) in Le Havre (IQR=23.9, 1-day lag). BS total mortality RRs per IQR were 0.5% (-1.8, 2.9) in Rouen (IQR=14.2, 1-day lag) and 0.3% (-1.6, 2.2) in Le Havre (IQR=11.5, 0-1 day lag avg.).
Roemer et al. (2001). Amsterdam. 1987-1998. BS and PM_{10} means in "background" = 10 and 39; BS mean in "traffic" area = 21. (No PM10 measurements available at traffic sites)	Daily deaths for those who lived along roads with more than 10,000 motor vehicle, as well as deaths for total population, were analyzed using data from background and traffic monitors. Poisson GAM model was used adjusting for season, day-of-week, and weather. BS, PM_{10}, SO_2, NO_2, CO, and O3 were analyzed.	Correlations between the background monitors and traffic monitors were moderate for BS (r = 0.55) but higher for NO_2 (r = 0.79) and O_3 (r = 0.80). BS and NO_2 were associated with mortality in both total and traffic population. Estimated RR for traffic population using background sites was larger than the RR for total population using background sites. The RR for total pop. using traffic sites was smaller that RRs for total population using background sites. This is not surprising since the mean BS for traffic sites were larger that for background sites.	The RRs per 100 ug/m3 BS (at lag 1-day) were 1.383 (1.153, 1.659), 1.887 (1.207, 2.949), and 1.122 (1.023, 1.231) for total population using background sites, traffic population using background sites, and total population using traffic sites, respectively. Results for traffic pop. using traffic sites not reported)

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Anderson et al. (2001). The west Midlands conurbation, UK. 1994-1996. PM means: PM_{10} = 23, $PM_{2.5}$ = 15, $PM_{10-2.5}$ = 9, BS = 13.2, sulfate = 3.7.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (avg. lag 0 and 1 days) were 0.2% (-1.8, 2.2) per 24.4 ug/m³ PM_{10}, 0.6% (-1.5, 2.7) per 17.7 ug/m³ $PM_{2.5}$, and –0.6% (-4.2, 2.3) per 11.3 ug/m³ $PM_{10-2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
Keatinge and Donaldson (2001). Greater London, England, 1976-1995. BS mean = 17.7.	The study examined potential confounding effects of atypical cold weather on air pollution/mortality relationships. First, air pollution variables (SO_2, CO and BS) were modeled as a function of lagged weather variables These variables were deseasonalized by regressing on seine and cosine variables. Mortality regression included various lagged and averaged weather and pollution variables. Analyses were conducted in the linear range of mortality/temperature relationship (15 to 0 degrees C).	Polluted days were found to be colder and less windy and rainy than usual. In the regression of mortality on the multiple-lagged temperature, wind, rain, humidity, sunshine, SO_2, CO, and BS, cold temperature was associated with mortality increase, but not SO_2 or CO. BS suggestive evidence, though not statistically significant, of association at 0- and 1-day lag.	3% (95% CI not reported) increase in daily mortality per 17.7 ug/m3 of BS (lag 0 and 1).
Latin America			
Cifuentes et al. (2000). Santiago, Chile. 1988-1996. $PM_{2.5}$ (64.0), and $PM_{10-2.5}$ (47.3).	Non-accidental total deaths (56.6 per day) were examined for associations with $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, SO_2, and NO_2. Data analyzed using GAM Poisson regression models, adjusting for temperature, seasonal cycles. Single and two pollutant models with lag days from 0 to 5, as well as the 2- to 5-day average concentrations evaluated.	Both PM size fractions associated with mortality, but different effects found for warmer and colder months. $PM_{2.5}$ and $PM_{10-2.5}$ both important in whole year, winter, and summer. In summer, $PM_{10-2.5}$ had largest effect size estimate. NO_2 and CO also associated with mortality, as was O_3 in warmer months. No consistent SO_2-mortality associations.	Percent excess total deaths per 25 $\mu g/m^3$ increase in the average of previous two days for the whole year: 1.8 (1.3, 2.4) for $PM_{2.5}$ and 2.3 (1.4, 3.2) for $PM_{10-2.5}$ in single pollutant models.
Castillejos et al. (2000). Mexico City. 1992-1995. PM_{10} (44.6), $PM_{2.5}$ (27.4), and $PM_{10-2.5}$ (17.2).	Non-accidental total deaths, deaths for age 65 and over, and cause-specific (cardiac, respiratory, and the other remaining) deaths were examined for their associations with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, and NO_2. Data were analyzed using GAM Poisson regression models, adjusting for temperature (average of 1-3 day lags) and seasonal cycles. Individual pollution lag days from 0 to 5, and average concentrations of previous 5 days were considered.	All three particle size fractions were associated individually with mortality. The effect size estimate was largest for $PM_{10-2.5}$. The effect size estimate was stronger for respiratory causes than for total, cardiovascular, or other causes of death. The results were not sensitive to additions of O_3 and NO_2. In the model with simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$, the effect size for $PM_{10-2.5}$ remained about the same, but the effect size for $PM_{2.5}$ became negligible.	Total mortality percent increase estimates per increase for average of previous 5 days: 9.5 (5.0, 14.2) for 50 $\mu g/m^3$ PM_{10}; 3.7 (0, 7.6) for 25 $\mu g/m^3$ $PM_{2.5}$; and 10.5 (6.4, 14.8) for 25 $\mu g/m^3$ $PM_{10-2.5}$.
Loomis et al. (1999). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27.4 $\mu g/m^3$)	Infant mortality (avg. ≈ 3/day) related to $PM_{2.5}$, O_3, and NO_2, adjusting for temperature and smoothed time, using Poisson GAM model.	Excess infant mortality associated with $PM_{2.5}$, NO_2, and O_3 in the same average/lags. NO_2 and O_3 associations less consistent in multi-pollutant models.	Infant mortality excess risk: 18.2% (6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$ at avg. 3-5 lag days.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America (cont'd)			
Borja-Aburto et al. (1998). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27)	Total, respiratory, cardiovascular, other deaths, and age-specific (age >= 65) deaths were related to $PM_{2.5}$, O_3, and NO_2, adjusting for 3-day lagged temperature and periodic cycles, using Poisson GAM model.	$PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 avg.; 1-5 avg., respectively). $PM_{2.5}$ associations were most consistently significant. SO_2 was available, but not analyzed because of its "low" levels.	For total excess deaths, 3.4% (0.4, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$ for both 0 and 4 d lags. For respiratory (4 d) = 6.4 (-2.6, 16.2); for CVD (4 d) = 5.6 (-0.1, 11.5)
Borja-Aburto et al. (1997). Mexico-City, 1990-1992. TSP (median: 204)	Total, respiratory, cardiovascular, and age-specific (age >= 65) deaths were related to O_3, TSP, and CO, adjusting for minimum temperature (temperature also fitted seasonal cycles) using Poisson models. The final models were estimated using the iteratively weighted and filtered least squares method to account for overdispersion and autocorrelation.	O_3, SO_2, and TSP were all associated with total mortality in separate models, but in multiple pollutant model, only TSP remained associated with mortality. CO association weak.	Total deaths: 6% (3.3, 8.3) per 100 $\mu g/m^3$ TSP at 0 d lag. CVD deaths: 5.2% (0.9, 9.9). Resp. deaths: 9.5% (1.3, 18.4).
Tellez-Rojo et al. (2000). Mexico City. 1994. PM10 mean = 75.1.	One year of daily total respiratory and COPD mortality series were analyzed for their associations with PM10 and O3 using Poisson model adjusting for cold or warm months, and 1-day lagged minimum temperature. The data were stratified by the place of deaths.	The average number of daily respiratory deaths, as well as that of COPD deaths, was similar for in and out of hospital. They found that the estimated PM_{10} relative risks were consistently larger for the deaths that occurred outside medical units. The results are apparently consistent with the assumption that the extent of exposure misclassification may be smaller for those who died outside medical units.	Percent excess for total respiratory and COPD mortality were 2.9% (0.9, 4.9) and 4.1% (1.3, 6.9) per 10 ug/m^3 increase in 3-day lag PM_{10},
Pereira et al. (1998). Sao Paulo, Brazil, 1991-1992. PM_{10} (beta-attenuation, 65)	Intrauterine mortality associations with PM_{10}, NO_2, SO_2, CO, and O_3 investigated using Poisson regression adjusting for season and weather. Ambient CO association with blood carboxyhemoglobin sampled from umbilical cords of non-smoking pregnant mothers studied in separate time period.	NO_2, SO_2, and CO were all individually significant predictor of the intrauterine mortality. NO_2 was most significant in multi-pollutant model. PM_{10} and O_3 were not significantly associated with the mortality. Ambient CO levels were associated with and carboxyhemoglobin of blood sampled from the umbilical cords.	Intrauterine mortality excess risk: 4.1% (-1.8, 10.4) per 50 $\mu g/m^3$ PM_{10} at 0 day lag.
Gouveia and Fletcher (2000). Sao Paulo, Brazil. 1991-1993. PM_{10} mean = 64.3.	All non-accidental causes, cardiovascular, and respiratory mortality were analyzed for their associations with air pollution (PM_{10}, SO_2, NO_2, O_3, and CO) using Poisson model adjusting for trend, seasonal cycles, and weather. Potential roles of age and socio-economic status were examined by stratifying data by these factors.	There was an apparent effect modification by age categories. Estimated PM_{10} effects were higher for deaths above age 65 (highest for the age 85+ category), and no associations were found in age group < 65 years. Respiratory excess deaths were larger than those for cardiovascular or non-accidental deaths. Other pollutants were also associated with the elderly mortality.	Percent excess for total non-accidental, cardiovascular, and respiratory mortality for those with age > 65 were 3.3% (0.6, 6.0), 3.8% (0.1, 7.6), and 6.0 (0.5, 11.8), respectively, per 64.2 ug/m^3 increase in PM_{10} (0-, 0-, and 1-day lag, respectively).
Conceicao et al. (2001). Sao Paulo, Brazil. 1994-1997. PM_{10} mean = 66.2	Daily respiratory deaths for children under 5 years of age were analyzed for their associations with air pollution (PM_{10}, SO_2, O_3, and CO) using GAM Poisson model adjusting for seasonal cycles and weather.	Significant mortality associations were found for CO, SO_2, and PM_{10} in single pollutant models. When all the pollutants were included, PM_{10} coefficient became negative and non-significant.	Percent excess for child (age < 5) respiratory deaths: 9.7% (1.5, 18.6) per 66.2 ug/m3 PM_{10} (2-day lag) in single pollutant model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Australia			
Morgan et al. (1998). Sydney, 1989-1993. Nephelometer (0.30 bscat/104m). Site-specific conversion: $PM_{2.5} \approx 9$; $PM_{10} \approx 18$	Total, cardiovascular, and respiratory deaths were related to PM (nephelometer), O_3, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation.	PM, O_3, and NO_2 all showed significant associations with total mortality in single pollutant models. In multiple pollutant models, the PM and O_3 effect estimates for total and cardiovascular deaths were marginally reduced, but the PM effect estimate for respiratory deaths was substantially reduced.	4.7% (1.6, 8.0) per 25 $\mu g/m^3$ estimated $PM_{2.5}$ or 50 $\mu g/m^3$ estimated PM_{10} at avg. of 0 and 1 day lags. (Note: converted from nephelometry data)
Simpson et al. (1997). Brisbane, 1987-1993. PM_{10} (27, not used in analysis). Nephelometer (0.26 bscat/104m, size range: 0.01-2 μm).	Total, cardiovascular, and respiratory deaths (also by age group) were related to PM (nephelometer), O_3, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation. Season-specific (warm and cold) analyses were also conducted.	Same-day PM and O_3 were associated most significantly with total deaths. The O_3 effect size estimates for cardiovascular and respiratory deaths were consistently positive (though not significant), and larger in summer. PM's effect size estimates were comparable for warm and cold season for cardiovascular deaths, but larger in warm season for respiratory deaths. NO_2 and SO_2 were not associated with mortality.	3.4% (0.4, 6.4) per 25 $\mu g/m^3$ 1-h $PM_{2.5}$ increment at 0 d lag; and 7.8% (2.5, 13.2) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.
Asia			
Hong et al. (1999). Inchon, South Korea, 1995-1996 (20 months). PM_{10} mean = 71.2.	Non-accidental total deaths, cardiovascular, and respiratory deaths were examined for their associations with PM_{10}, O_3, SO_2, CO, and NO_2. Data were analyzed using GAM Poisson regression models, adjusting for temperature, relative humidity, and seasonal cycles. Individual pollution lag days from 0 to 5, as well as the average concentrations of previous 5 days were considered.	A greater association with mortality was seen with the 5-day moving average and the previous day's exposure than other lag/averaging time. In the models that included a 5-day moving average of one or multiple pollutants, PM_{10} was a significant predictor of total mortality, but gaseous pollutants were not significant. PM_{10} was also a significant predictor of cardiovascular and respiratory mortality.	Percent excess deaths (t-ratio) per 50 $\mu g/m^3$ increase in the 5-day moving average of PM_{10}: 4.1 (0.1, 8.2) for total deaths; 5.1 (0.1, 10.4) for cardiovascular deaths; 14.4 (−3.2, 35.2) for respiratory deaths.
Lee et al. (1999). Seoul and Ulsan, Korea, 1991-1995. TSP (beta attenuation, 93 for Seoul and 72 for Ulsan)	Total mortality series was examined for its association with TSP, SO_2, and O_3, in Poisson GEE (exchangeable correlation for days in the same year), adjusting for season, temperature, and humidity.	All the pollutants were significant predictors of mortality in single pollutant models. TSP was not significant in multiple pollutant models, but SO_2 and O_3 remained significant.	5.1% (3.1, 7.2) for Seoul, and -0.1% (-3.9, 3.9) for Ulsan, per 100 $\mu g/m^3$ TSP at avg. of 0, 1, and 2 day lags.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Lee and Schwartz (1999). Seoul, Korea. 1991-1995. TSP mean = $9_{2.5}$.	Total deaths were analyzed for their association with TSP, SO_2, and O_3. A conditional logistic regression analysis with a case-crossover design was conducted. Three-day moving average values (current and two past days) of TSP and SO_2, and 1-hr max O_3 were analyzed separately. The control periods are 7 and 14 days before and/or after the case period. Both unidirectional and bi-directional controls (7 or 7 and 14 days) were examined, resulting in six sets of control selection schemes. Other covariates included temperature and relative humidity.	Among the six control periods, the two unidirectional retrospective control schemes resulted in odds ratios less than 1; the two unidirectional prospective control schemes resulted in larger odds ratios (e.g., 1.4 for 50 ppb increase in SO_2); and bi-directional control schemes resulted in odds ratios between those for uni-directional schemes. SO_2 was more significantly associated with mortality than TSP.	OR for non-accidental mortality per 100 $\mu g/m^3$ increase in 3-day average TSP was 1.010 (0.988, 1.032).
Xu et al. (2000). Shenyang, China, 1992. TSP (430).	Total (non-accidental), CVD, COPD, cancer and other deaths examined for their associations with TSP and SO_2,using Poisson (GAM, and Markov approach to adjust for mortality serial dependence) models, adjusting for seasonal cycles, Sunday indicator, quintiles of temp. and humidity. Ave. pollution values of concurrent and 3 preceding days used.	Total deaths were associated with TSP and SO_2 in both single and two pollutant models. TSP was significantly associated with CVD deaths, but not with COPD. SO_2 significantly associated with COPD, but not with CVD deaths. Cancer deaths not associated with TSP or SO_2.	Percent total excess deaths per 100 $\mu g/m^3$ increase in 0-3 day ave. of TSP = 1.75 (0.65, 2.85); with SO_2 = 1.31 (0.14, 2.49) COPD TSP = 2.6 (−0.58, 5.89); with SO_2 = 0.76 (−2.46, 4.10). CVD TSP = 2.15 (0.56, 3.71); with SO_2 = 1.95 (1.19, 3.74). Cancer TSP = 0.87 (−1.14, 2.53); with SO_2 = 1.07 (−1.05, 3.23). Other deaths TSP = 3.52 (0.82, 6.30); with SO_2 = 2.40 (−0.51, 5.89).
Ostro et al. (1998). Bangkok, Thailand, 1992-1995 PM_{10} (beta attenuation, 65)	Total (non-accidental), cardiovascular, respiratory deaths examined for associations with PM_{10} (separate measurements showed ≈50% of PM_{10} was $PM_{2.5}$),using Poisson GAM model adjusting for seasonal cycles, day-of-week, temp., humidity.	All the mortality series were associated with PM_{10} at various lags. The effects appear across all age groups. No other pollutants were examined.	Total mortality excess risk: 5.1% (2.1, 8.3) per 50 $\mu g/m^3$ PM_{10} at 3 d lag (0 and 2 d lags also significant). CVD (3 d ave.) = 8.3 (3.1, 13.8) Resp. (3 d ave.) = 3.0 (−8.4, 15.9)

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Cropper et al. (1997). Delhi, India, 1991-1994 TSP (375)	Total (by age group), respiratory and CVD deaths related to TSP, SO_2, and NOx, using GEE Poisson model (to control for autocorrelation), adjusting for seasonal cycles (trigonometric terms), temperature, and humidity. 70% deaths occur before age 65 (in U.S., 70% occur after age 65).	TSP was significantly associated with all mortality series except with the very young (age 0-4) and the "very old" (age >=65). The results were reported to be unaffected by addition of SO_2 to the model. The authors note that, because those who are affected are younger (than Western cities), more life-years are likely to be lost per person from air pollution impacts.	2.3% (significant at 0.05, but SE of estimate not reported) per 100 $\mu g/m^3$ TSP at 2 day lag.
Kwon et al. (2001). Seoul, South Korea, 1994-1998. PM10 mean = 68.7.	The study was planned to test the hypothesis that patients with congestive heart failure are more susceptible to the harmful effects of ambient air pollution than the general population. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week, as well as the case-crossover design, with 7 and 14 days before and after the case period, were applied	The estimated effects were larger among the congestive heart failure patients than among the general population (2.5 ~ 4.1 times larger depending on the pollutants). The case-crossover analysis showed similar results. In two pollutant models, the PM_{10} effects were much lower when CO, NO_2, or SO_2 were included. O_3 had little impact on the effects of the other pollutants.	The RRs for PM_{10} (same-day) using the GAM approach for the general population and for the cohort with congestive heart failure were 1.4% (0.6, 2.2) and 5.8 (-1.1, 13.1), respectively, per 42.1 ug/m3. Corresponding ORs using the case-crossover approach were 0.1% (-0.9, 1.2) and 7.4% (-2.2, 17.9), respectively.
Lee et al. (2000). Seven major cities, Korea. 1991-1997. TSP mean = 77.9.	All non-accidental deaths were analyzed for their associations with TSP, SO_2, NO_2, O_3, and CO using GAM Poisson model adjusting for trend, seasonal cycles, and weather. Pollution relative risk estimates were obtained for each city, and then pooled.	In the results of pooled estimates for multiple pollutant models, the SO_2 relative risks were not affected by addition of other pollutants, whereas the relative risks for other pollutants, including TSP, were. The SO_2 levels in these Korean cities were much higher than the levels observed in the current U.S. For example, the 24-hr mean SO_2 levels in the Korean cities ranged from 12.1 to 31.4 ppb, whereas, in Samet et al.'s 20 largest U.S. cities, the range of 24-hr mean SO_2 levels were 0.7 to 12.8 ppb.	Percent excess deaths for all non-accidental deaths was 1.7% (0.8, 2.6) per 100 ug/m³ 2-day moving average TSP.

APPENDIX 8B

PARTICULATE MATTER-MORBIDITY STUDIES: SUMMARY TABLES

Appendix 8B.1: PM-Cardiovascular Admissions Studies

TABLE 8B-1. ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes. Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States			
Samet et al. (2000a,b) 14 US cities 1985-1994, but range of years varied by city PM_{10} ($\mu g/m^3$) mean, median, IQR: Birmingham, AL: 34.8, 30.6, 26.3 Boulder, CO: 24.4, 22.0, 14.0 Canton, OH: 28.4, 25.6, 15.3 Chicago, Il: 36.4, 32.6, 22.4 Colorado Springs, CO: 26.9, 22.9, 11.9 Detroit, MI: 36.8, 32.0, 28.2 Minneapolis/St. Paul, MN: 27.4, 24.1, 17.9 Nashville, TN: 31.6, 29.2, 17.9 New Haven, CT: 29.3, 26.0, 20.2 Pittsburgh, PA: 36.0, 30.5, 27.4 Provo/Orem, UT: 38.9, 30.3, 22.8 Seattle, WA: 31.0, 26.7, 20.0 Spokane, WA: 45.3, 36.2, 33.5 Youngstown, OH: 33.1, 29.4, 18.6	Daily medicare hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Mean CVD counts ranged from 3 to 102/day in the 14 cities. Covariates: SO_2, NO_2, O_3, CO, temperature, relative humidity, barometric pressure. Stats: In first stage, performed city-specific, PM10-ONLY, generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 14 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and slopes of PM_{10} on co-pollutants.	City-specific risk estimates for a 10 $\mu g/m^3$ increase in PM_{10} ranged from -1.2% in Canton to 2.2% in Colorado Springs. Across-city weighted mean risk estimate was largest at lag 0, diminishing rapidly at other lags. Only the mean of lags 0 and 1 was significantly associated with CVD. There was no evidence of statistical heterogeniety in risk estimates across cities for CVD. City-specific risk estimates were not associated with the percent of the population that was non-white, living in poverty, college educated, nor unemployed. No evidence was observed that PM_{10} effects were modified by weather. No association was observed between the city-specific PM_{10} risk estimates and the city-specific correlation between PM_{10} and co-pollutants. However, due to the absence of multi-pollutant regression results, it is not clear whether this study demonstrates an independent effect of PM_{10}.	Percent Excess CVD Risk (95% CI), combined over cities per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d lag. 5.5% (4.7, 6.2) PM_{10}: 0–1d lag. 6.0% (5.1, 6.8) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d lag. 7.6% (6.0, 9.1)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Janessen et al. (2002) 14 U.S. cities studied in Samet et al. (2000a,b) above	Examined same database as Samet et al. (2000a,b) to evaluate whether differences in prevalence in air conditioning (AC) and/or the contribution of different sources to total PM_{10} emissions could partially explain the observed variability in exposure effect relations. Variables included 24-hr means of temperature. Cities were characterized and analyzed as either winter or nonwinter peaking. Rations between mean concentrations during summer (June, July August) and winter (January, February, March) were calculated. (*Winter peaking PM_{10} concentration.)	Analysis of city groups of winter peaking, PM_{10} and nonwinter peaking PM_{10} yielded coefficients for CVD-related hospitalization admissions that decreased significantly with increasing percentage of central AC for both city groups. Four source related variables coefficients for hospital admissions for CVD increased significantly with increasing percentage of PM_{10} from highway vehicles, highway diesels, oil combustion, metal processing, increasing population, and vehicle miles traveled (VMT) per sq mg and with decreasing percentage of PM_{10} from fugitive dust. For COPD and pneumonia association were less significant but the pattern of association were similar to that for CVD.	**Homes with AC** β CVD % change (SE) All cities −15.2 (14.8) Nonwinter peak cities −50.3** (17.4) Winter peak cities −51.7** (13.8) **Source PM_{10} from highway vehicles** % change (SE) β CVD 58.0* (9.9) [**p <0.05]

PM₁₀ (μg/m³) / Mean Summer/Winter / Ratio

PM_{10} (μg/m³)	Mean Summer/Winter	Ratio
Birmingham	40.0/27.4	0.69
Boulder*	26.8/36.3	1.35
Canton	36.6/25.8	0.70
Chicago	42.5/30.4	0.71
Colorado Springs*	21.3/37.3	1.75
Detroit	42.8/32.8	0.77
Minneapolis	30.5/23.0	0.75
Nashville	40.1/31.9	0.80
New Haven	30.3/31.6	1.04
Pittsburgh	46.6/29.4	0.63
Seattle*	23.8/43.3	1.82
Spokane*	32.7/42.2	1.29
Provo-Urem*	31.4/66.3	2.11
Youngstown	40.7/30.1	0.74

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description	Results and Comments	PM Index, Lag, Excess Risk %
Zanobetti et al. (2000b) 10 US cities 1986-1994 PM_{10} (μg/m³) median, IQR: Canton, OH: 26, 15 Birmingham, AL: 31, 26 Chicago, Il: 33, 23 Colorado Springs, CO: 23, 13 Detroit, MI: 32, 28 Minneapolis/St. Paul, MN: 24, 18 New Haven, CT: 26, 21 Pittsburgh, PA: 30, 28 Seattle, WA: 27, 21 Spokane, WA: 36, 34	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Median CVD counts ranged from 3 to 103/day in the 10 cities. Covariates: SO_2, O_3, CO, temperature, relative humidity, barommetric pressure. Stats: In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 μg/m³ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 μg/m³. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. As with Samet et al. 2000., it is not clear whether this study demonstrates an independent effect of PM_{10}.	Percent Excess Risk (SE) combined over cities: Effects computed for 50 μg/m³ change in PM_{10}. PM_{10}: 0 d. 5.6 (4.7, 6.4) PM_{10}: 0–1 d. 6.2 (5.4, 7.0) PM_{10} < 50 μg/m³: 0–1 d. 7.8 (6.2, 9.4)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Schwartz (1999) 8 US metropolitan counties 1988-1990 median, IQR for PM_{10} ($\mu g/m^3$): Chicago, IL: 35, 23 Colorado Springs, CO: 23, 14 Minneapolis, MN: 28, 15 New Haven, CT: 37, 25 St. Paul, MN: 34, 23 Seattle, WA: 29, 20 Spokane, WA: 37, 33 Tacoma, WA: 37, 27	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Median daily hospitalizations: 110, 3, 14, 18, 9, 22, 6, 7, alphabetically by city. Covariates: CO, temperature, dewpoint temp. Stats: robust Poisson regression after removing admission outliers; generalized additive models with LOESS smooths for control of trends, seasons, and weather. Day of week dummy variables. Lag 0 used for all covariates.	In single-pollutant models, similar PM_{10} effect sizes obtained for each county. Five of eight county-specific effects were statistically significant, as was the PM_{10} effect pooled across locations. CO effects significant in six of eight counties. The PM_{10} and CO effects were both significant in a two pollutant model that was run for five counties where the PM_{10}/CO correlation was less than 0.5. Results reinforce those of Schwartz, 1997.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0d. Individual counties: Chicago: 4.7 (2.6, 6.8) CO Spng: 5.6 ($-$6.8, 19.0) Minneap: 4.1 ($-$3.6, 12.5) New Hav: 5.8 (2.1, 9.7) St. Paul: 8.6 (2.9, 14.5) Seattle: 3.6 ($-$0.1, 7.4) Spokane: 6.7 (0.9, 12.8) Tacoma: 5.3 (3.1, 7.6) Pooled: 5.0 (3.7, 6.4) 3.8 (2.0, 5.5) w. CO
Linn et al. (2000) Los Angeles 1992-1995 mean, SD: $PM_{10\ est}$ ($\mu g/m^3$): 45, 18	Hospital admissions for total cardiovascular diseases (CVD), congestive heart failure (CHF), myocardial infarction (MI), cardiac arrhythmia (CA) among all persons 30 years and older, and by sex, age, race, and season. Mean hospital admissions for CVD: 428. Covariates: CO, NO_2, O_3, temperature, rainfall. Daily gravimetric PM_{10} estimated by regression of every sixth day PM_{10} on daily real-time PM_{10} data collected by TEOM. Poisson regression with controls for seasons and day of week. Reported results for lag 0 only. Results reported as Poisson regression coefficients and their standard errors. The number of daily CVD admissions associated with the mean PM_{10} concentration can be computed by multiplying the PM_{10} coefficient by the PM_{10} mean and then exponentiating. Percent effects are calculated by dividing this result by the mean daily admission count for CVD.	In year-round, single-pollutant models, significant effects of CO, NO_2, and PM_{10} on CVD were reported. PM_{10} effects appeared larger in winter and fall than in spring and summer. No consistent differences in PM_{10} effects across sex, age, and race. CO risk was robust to including PM_{10} in the model; no results presented on PM_{10} robustness to co-pollutants.	% increase with PM_{10} change of 50 $\mu g/m^3$: $PM_{10\ est}$: 0 d. CVD ages 30+ 3.25% (2.04, 4.47) MI ages 30+ 3.04% (0.06, 6.12) CHF ages 30+ 2.02% ($-$0.94, 5.06) CA ages 30+ 1.01% ($-$1.93, 4.02)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			

Morris and Naumova (1998) Chicago, IL 1986-1989 mean, median, IQR, 75th percentile: PM_{10} ($\mu g/m^3$): 41, 38, 23, 51	Daily hospital admissions for congestive heart failure, CHF (ICD9 428), among persons over 65 years. Mean hospitalizations: 34/day. Covariates: O_3, NO_2, SO_2, CO, temperature, relative humidity. Gases measured at up to eight sites; daily PM_{10} measured at one site. Stats: GLM for time series data. Controlled for trends and cycles using dummy variables for day of week, month, and year. Residuals were modeled as negative binomial distribution. Lags of 0-3 days examined.	CO was only pollutant statistically significant in both single- and multi-pollutant models. Exposure misclassification may have been larger for PM_{10} due to single site. Results suggest effects of both CO and PM_{10} on congestive heart failure hospitalizations among elderly, but CO effects appear more robust.	Percent Excess Risk (95% CI) per 50 $\mu g/m^3$ change in PM_{10}.
			
			PM_{10}: 0 d.
			  3.92% (1.02, 6.90)
			  1.96% (−1.4, 5.4) with
			    4 gaseous pollutants

Schwartz (1997) Tucson, AZ 1988-1990 mean, median, IQR: PM_{10} ($\mu g/m^3$): 42, 39, 23	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Mean hospitalizations: 13.4/day. Covariates: O_3, NO_2, CO, SO_2, temperature, dewpoint temperature. Gases measured at multiple sites; daily PM_{10} at one site. Stats: robust Poisson regression; generalized additive model with LOESS smooth for controlling trends and seasons, and regression splines to control weather. Lags of 0-2 days examined.	Both PM_{10} (lag 0) and CO significantly and independently associated with admissions, whereas other gases were not. Sensitivity analyses reinforced these basic results. Results suggest independent effects of both PM_{10} and CO for total cardiovascular hospitalizations among the elderly.	Percent Excess Risk (95% CI) per 50 $\mu g/m^3$ change in PM_{10}.
			
			PM_{10}: 0 d.
			  6.07% (1.12, 1.27)
			  5.22% (0.17, 10.54) w. CO

Gwynn et al (2000) Buffalo, NY mn/max PM_{10} = 24.1/90.8 $\mu g/m^3$ SO_4^- = 2.4/3.9 H^+ = 36.4/38.2 nmol/m^3 CoH = 0.2/0.9 10^{-3} ft	Air pollution health effects associations with total, respiratory, and CVD hospital admissions (HA's) examined using Poisson model controlling for weather, seasonality, long-wave effects, day of week, holidays.	Positive, but non-significant assoc. found between all PM indices and circulatory hospital admissions. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates.	Percent excess CVD HA risks (95% CI) per PM_{10} = 50 $\mu g/m^3$; SO_4 = 15 $\mu g/m^3$; H^+ = 75 nmoles/m^3; COH = 0.5 units/1,000 ft: PM_{10} (lag 3) = 5.7% (−3.3, 15.5) SO_4 (lag 1) = 0.1% (−0.1, 0.4) H^+ (lag 0) = 1.9% (−0.3, 4.2) COH (lag 1) = 2.2% (−1.9, 6.3)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR $\mu g/m^3$	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Lippmann et al. (2000) Detroit, MI 1992-1994 mean, median, IQR: $PM_{2.5}$ ($\mu g/m^3$): 18, 15, 11 PM_{10} ($\mu g/m^3$): 31, 28, 19 $PM_{10-2.5}$ ($\mu g/m^3$): 13, 12, 9	Various cardiovascular (CVD)-related hospital admissions (HA's) for persons 65+ yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 $nmol/m^3$).	For heart failure, all PM metrics yielded significant associations. Associations for IHD, dysrhythmia, and stroke were positive but generally non-sig. with all PM indices. Adding gaseous pollutants had negligible effects on various PM metric RR estimates. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per $\mu g/m^3$ in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity not usually present. However, small sample size limits power to distinguish between pollutant-specific effects.	Percent excess CVD HA risks (95% CI) per 50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$: IHD: $\quad PM_{2.5}$ (lag 2) 4.3 (−1.4, 10.4) $\quad PM_{10}$ (lag 2) 8.9 (0.5, 18.0) $\quad PM_{10-2.5}$ (lag 2) 10.5 (2.7, 18.9) Dysrhythmia: $\quad PM_{2.5}$ (lag 1) 3.2 (−6.5, 14.0) $\quad PM_{10}$ (lag 1) 2.9 (−6.8, 13.7) $\quad PM_{10-2.5}$ (lag 0) 0.2 (−12.2, 14.4) Heart Failure: $\quad PM_{2.5}$ (lag 1) 9.1 (2.4, 16.2) $\quad PM_{10}$ (lag 0) 9.7 (0.2, 20.1) $\quad PM_{10-2.5}$ (lag 0) 5.2 (−3.3, 14.5) Stroke: $\quad PM_{2.5}$ (lag 0) 1.8 (−5.3, 9.4) $\quad PM_{10}$ (lag 1) 4.8 (−5.5, 16.2) $\quad PM_{10-2.5}$ (lag 1) 4.9 (−4.7, 15.5)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Moolgavkar (2000b) Three urban counties: Cook, IL; Los Angeles, CA; Maricopa, AZ. 1987-1995 Pollutant median, IQR: Cook: PM_{10}: 35, 22 LA: PM_{10}: 44, 26 $PM_{2.5}$: 22, 16 Maricopa: PM_{10}: 41, 19	Analysis of daily hospital admissions for total cardiovascular diseases, CVD, (ICD9 codes 390-429) and cerebrovascular diseases, CRD, (ICD9 430-448) among persons aged 65 and over. For Los Angeles, a second age group, 20-64, was also analyzed. Median daily CVD admissions were 110, 172, and 33 in Cook, LA, and Maricopa counties, respectively. PM_{10} available only every sixth day in LA and Maricopa counties. In LA, every-sixth-day $PM_{2.5}$ also was available. Covariates: CO, NO_2, O_3, SO_2, temperature, relative humidity. Stats: generalized additive Poisson regression, with controls for day of week and smooth temporal variability. Single-pollutant models estimated for individual lags from 0 to 5. Two-pollutant models also estimated, with both pollutants at same lag.	In single-pollutant models in Cook and LA counties, PM was significantly associated with CVD admissions at lags 0, 1, and 2, with diminishing effects over lags. $PM_{2.5}$ also was significant in LA for lags 0 and 1. For the 20-64 year old age group in LA, risk estimates were similar to those for 65+. In Maricopa county, no positive PM_{10} associations were observed at any lag. In two-pollutant models in Cook and LA counties, the $PM_{10}/PM_{2.5}$ risk estimates diminished and/or were rendered non-significant. Little evidence observed for associations between CRD admissions and PM. These results suggest that PM is not independently associated with CVD or CRD hospital admissions.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ change in PM_{10} and 25 $\mu g/m^3$ change in $PM_{2.5}$. Cook 65+: PM_{10}, 0 d. 4.2 (3.0, 5.5) PM_{10}, 0 d. w/NO_2. 1.8 (0.4, 3.2) LA 65+: PM_{10}, 0 d. 3.2 (1.2, 5.3) PM_{10}, 0 d. w/CO -1.8 (-4.4, 0.9) $PM_{2.5}$, 0 d. 4.3 (2.5, 6.1) $PM_{2.5}$, 0 d. w/CO 0.8 (-1.3, 2.9) LA 20$-$64 years old: PM_{10}, 0 d. 4.4 (2.2, 6.7) PM_{10}, 0 d. w/CO 1.4 (-1.3, 4.2) $PM_{2.5}$, 0 d. 3.5 (1.8, 5.3) $PM_{2.5}$, 0 d., w/CO) 2.3 (-0.2, 4.8) Maricopa: PM_{10}, 0 d. -2.4 (-6.9, 2.3)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Zanobetti et al. (2000a) Cook County, IL 1985-1994 Median, IQR: PM_{10} ($\mu g/m^3$): 33, 23	Total cardiovascular hospital admissions in persons 65 and older (ICD 9 codes390-429) in relation to PM_{10}. Data were analyzed to examine effect modification by concurrent or preexisting cardiac and/or respiratory conditions, age, race, and sex. No co-pollutants included.	Evidence seen for increased CVD effects among persons with concurrent respiratory infections or with previous admissions for conduction disorders.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ PM_{10}, 0-1 D. AVG. CVD: 6.6 (4.9-8.3)
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} ($\mu g/m^3$): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} ($\mu g/m^3$): 29.1, 27.6, 12.0 $PM_{2.5}$ ($\mu g/m^3$): 19.4, 17.5, 9.35 CP ($\mu g/m^3$): 9.39, 8.95, 4.52 10-100 nm PM counts (count/cm^3): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals ($\mu g/m^3$): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates ($\mu g/m^3$): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity ($\mu g/m^3$): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM ($\mu g/m^3$): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon ($\mu g/m^3$): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for dysrhythmias, DYS, (ICD 9 code 427) and all cardiovascular diseases, CVD, (codes 402, 410-414, 427, 428, 433-437, 440, 444, 451-453) for persons aged 16 and older in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all CVD in period 1 were 6.5 and 28.4, respectively. Mean daily ED visits for dysrhythmias and all CVD in period 2 were 11.2 and 45.1, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day of week and hospital entry/exit indicators also included. Pollutants were treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, significant negative association (p=0.02) observed between CVD and 3-day average PM_{10}. There was ca. 2% drop in CVD per 10 $\mu g/m^3$ increase in PM_{10}. CVD was positively associated with NO_2 (p=0.11) and negatively associated with SO_2 (p=0.10). No association observed between dysrhythmias and PM_{10} in period 1. However, dysrhythmias were positively associated with NO_2 (p=0.06). In period 2, i.e., the first year of operation of the superstation, no associations seen with PM_{10} or $PM_{2.5}$. However, significant positive associations observed between CVD and elemental carbon (p=0.005) and organic matter (p=0.02), as well as with CO (p=0.001). For dysrhythmias, significant positive associations observed with elemental carbon (p=0.004), CP (p=0.04), and CO (p=0.005). These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Percent Excess Risk (p-value): Effects computed for 50 $\mu g/m^3$ change in PM_{10}; 25 $\mu g/m^3$ for CP and $PM_{2.5}$; 25,000 counts/cm^3 for 10-100 nm counts. Period 1: PM_{10}, 0-2 d. avg. CVD: −8.2 (0.02) DYS: 4.6 (0.58) Period 2: 0-2 d. avg. in all cases CVD % effect; DYS % effect: PM_{10}: 5.1 (−7.9, 19.9); 13.1 (−14.1, 50.0) $PM_{2.5}$: 6.1 (−3.1, 16.2); 6.1 (−12.6, 28.9) CP: 17.6 (−4.6, 45.0); 53.2 (2.1, 129.6) 10-100 nm counts: −11.0 (0.17); 3.0 (0.87)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada			
Burnett et al. (1995) Ontario, Canada 1983-1988 Sulfate Mean: 4.37 μg/m^3 Median: 3.07 μg/m^3 95th percentile: 13 μg/m^3	168 Ontario hospitals. Hospitalizations for coronary artery disease, CAD (ICD9 codes 410,413), cardiac dysrhythmias, DYS (code 427), heart failure, HF (code 428), and all three categories combined (total CVD). Mean total CVD rate: 14.4/day. 1986 population of study area: 8.7 million. All ages, <65, >=65. Both sexes, males, females. Daily sulfates from nine monitoring stations. Ozone from 22 stations. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. Day of week effects removed. 0-3 day lags examined. Covariates: ozone, ozone^2, temperature, temperature^2. Linear and quadratic sulfate terms included in model.	Sulfate lagged one day significantly assoc. with total CVD admissions with and without ozone in the model. Larger associations observed for coronary artery disease and heart failure than for cardiac dysrhythmias. Suggestion of larger associations for males and the sub-population 65 years old and greater. Little evidence for seasonal differences in sulfate effects after controlling for covariates.	Effects computed for 95th percentile change in SO$_4$ SO$_4$, 1d, no covariates: Total CVD: 2.8 (1.8, 3.8) CAD: 2.3 (0.7, 3.8) DYS: 1.3 (−2.0, 4.6) HF: 3.0 (0.6, 5.3) Males: 3.4 (1.8, 5.0) Females: 2.0 (0.2, 3.7) <65: 2.5 (0.5, 4.5) >=65: 3.5 (1.9, 5.0) SO$_4$, 1d, w. temp and O$_3$: Total CVD: 3.3 (1.7,4.8)
Burnett et al. (1997a) Canada's 10 largest cities 1981-1994 COH daily maximum Mean: 0.7 10^3 ln feet Median: 0.6 10^3 ln feet 95th percentile: 1.5 10^3 ln feet	Daily hospitalizations for congestive heart failure (ICD9 code 427) for patients over 65 years at 134 hospitals. Average hospitalizations: 39/day. 1986 population of study area: 12.6 million. Regressions on air quality using generalized estimating equations, controlling for long-term trends, seasonality, day of week, and inter-hospital differences. Models fit monthly and pooled over months. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. 0-3 day lags examined. Covariates: CO, SO$_2$, NO$_2$, O$_3$, temperature, dewpoint temperature.	COH significant in single-pollutant models with and without weather covariates. Only *ln*CO and *ln* NO$_2$ significant in multi-pollutant models. COH highly colinear with CO and NO$_2$. Suggests no particle effect independent of gases. However, no gravimetric PM data were included.	Effects computed for 95% change in COH: 0 d lag: 5.5% (2.5, 8.6) 0 d lag w/weather: 4.7% (1.3, 8.2) 0 d lag w/CO, NO$_2$, SO$_2$, O$_3$: −2.26 (−6.5, 2.2)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997b) Metro-Toronto, Canada 1992-1994 Pollutant: mean, median, IQR: COH (10^3 ln ft): 0.8, 0.8, 0.6 H+ (nmol/m^3): 5, 1, 6 SO$_4$ (nmol/m^3): 57, 33, 57 PM$_{10}$ (μg/m^3): 28, 25, 22 PM$_{2.5}$ (μg/m^3): 17, 14, 15 PM$_{10-2.5}$ (μg/m^3): 12, 10, 7	Daily unscheduled cardiovascular hospitalizations (ICD9 codes 410-414,427, 428) for all ages. Average hospital admissions: 42.6/day. Six cities of metro-Toronto included Toronto, North York, East York, Etobicoke, Scarborough, and York, with combined 1991 population of 2.36 million. Used same stat model as in Burnett et al., 1997c. 0- 4 day lags examined, as well as multi-day averages. Covariates: O$_3$, NO$_2$, SO$_2$, CO, temperature, dewpoint temperature.	Relative risks > 1 for all pollutants in univariate regressions including weather variables; all but H+ and FP statistically significant. In multivariate models, the gaseous pollutant effects were generally more robust than were particulate effects. However, in contrast to Burnett et al. (1997A), COH remained significant in multivariate models. Of the remaining particle metrics, CP was the most robust to the inclusion of gaseous covariates. Results do not support independent effects of FP, SO$_4$, or H+ when gases are controlled.	Percent excess risk (95% CI) per 50 μg/m^3 PM$_{10}$, 25 μg/m^3 PM$_{2.5}$, and PM$_{10-2.5}$, and IQR for other indicators. COH: 0–4 d. 6.2 (4.0, 8.4) 5.9 (2.8, 9.1) w. gases H+: 2–4 d. 2.4 (0.4, 4.5) 0.5 (−1.6, 2.7) w. gases SO$_4$: 2–4 d. 1.7 (−0.4, 3.9) −1.6 (−4.4, 1.3) w. gases PM$_{10}$: 1–4 d. 7.7 (0.9, 14.8) −0.9 (−8.3, 7.1) w. gases PM$_{2.5}$: 2–4 d. 5.9 (1.8, 10.2) −1.1 (−7.8, 6.0) w. gases PM$_{10-2.5}$: 0–4 d. 13.5 (5.5, 22.0) 8.1 (−1.3, 18.3) w. gases

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} ($\mu g/m^3$): 18, 16, 10 CP_{est} ($\mu g/m^3$): 12, 10, 8 $PM_{10\ est}$ ($\mu g/m^3$): 30, 27, 15	Daily hospitalizations for dysrhythmias, DYS (ICD9 code 427; mean 5/day); heart failure, HF (428; 9/d); ischemic heart disease, IHD (410-414; 24/d); cerebral vascular disease, CVD (430-438; 10/d); and diseases of the peripheral circulation, DPC (440-459; 5/d) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were <u>estimated</u>, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models used and non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in cardiac outcome (DVS, HF, IHD). No associations with vascular outcomes, except for CPest with DPC. In multi-pollutant models, PM effects estimates reduced by variable amounts (often >50%) for specific endpoints and no statistically significant (at p<0.05) PM associations seen with any cardiac or circulatory outcome (results not shown). Use of estimated PM metrics limits interpretation of pollutant-specific results. However, results suggest that linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when full range of gaseous pollutants also modeled.	Single pollutant models: Percent excess risk (95% CI) per 50 $\mu g/m^3$ PM_{10}; 25 $\mu g/m^3$ $PM_{2.5}$; and 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$. All cardiac HA (lags 2-5 d): $PM_{2.5}$ 1-poll = 8.1 (2.45, 14.1) $PM_{2.5}$ w/4 gases = −1.6 (−10.4, 8.2); w/CO = 4.60 (−3.39, 13.26) PM_{10} 1-poll = 12.07 (1.43, 23.81) w/4 gases = −1.40 (−12.53, 11.16) w/CO = 10.93 (0.11, 22.92) $PM_{10\text{-}2.5}$ 1-poll = 20.46 (8.24, 34.06) w/4 gases = 12.14 (−1.89, 28.2); w/CO = 19.85 (7.19, 34.0) <u>DYS:</u> FP_{est} (0 d): 6.1 (1.9, 10.4) CP_{est} (0 d): 5.2 (−0.21, 1.08) $PM_{10\ est}$: (0 d): 8.41 (2.89, 14.2) <u>HF:</u> FP_{est} (0−2 d): 6.59 (2.50, 10.8) CP_{est} (0−2 d): 7.9 (2.28, 13) $PM_{10\ est}$ (0−2 d): 9.7 (4.2, 15.5) <u>IHD:</u> FP_{est} (0−2 d): 8.1 (5.4, 10.8) CP_{est} (0 d): 3.7 (1.3, 6.3) $PM_{10\ est}$ (0−1 d): 8.4 (5.3, 11.5)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 **HOSPITAL ADMISSIONS** H+ (nmol/m^3): 25.7, 36.8 Sulfate (nmol/m^3): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for angina/myocardial infarction (mean 1.8/day), congestive heart failure (1.0/day), dysrhythmia/conduction disturbance (0.8/day), and all cardiac conditions (3.5/day) for persons of all ages. Covariates included CO, H$_2$S, NO$_2$, O$_3$, SO$_2$, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations observed between all cardiac ED visits and PM$_{10}$, PM$_{2.5}$, H$_2$S, O$_3$, and SO$_2$. Significant negative associations observed with H+, sulfate, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics were significantly associated with all cardiac ED visits in full year analyses, whereas both O$_3$ and SO$_2$ were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions. In cause-specific, single-pollutant models, PM tended to be positively associated with dysrhythmia/conductive disturbances but negatively associated with congestive heart failure (no quantitative results presented). The objective decision rule used for selecting lags reduced the risk of data mining; however, the biological plausibility of lag effects beyond 3-5 days is open to question. Rich co-pollutant data base. Results imply no effects of PM independent of co-pollutants.	Percent Excess Risk (p-value) computed for 50 $\mu g/m^3$ PM$_{10}$, 25 $\mu g/m^3$ PM$_{2.5}$ and mean levels of sulfate and COH. Full year results for all cardiac conditions, single pollutant models: PM$_{10}$: 3d. 29.3 (P=0.003) PM$_{2.5}$: 3d. 14.4 (P=0.055) H+: 4–9 d. avg. –1.8 (0.010) Sulfate: 4d. –6.0 (0.001) COH max: 7d. –5.4 (0.027) Full year results for all cardiac conditions, multi-pollutant models: No significant PM associations.

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe			
Le Tertre et al. (2002) Eight-City - APHEA 2 Study mean (SD) PM_{10} $\mu g/m^3$ Barcelona - 1/94-12/96 55.7 (18.4) Birmingham - 3/92-12/94 24.8 (13.1) London - 1/92-12/94 28.4 (12.3) Milan - No PM_{10} Netherlands - 1/92-9/95 39.5 (19.9) Paris - 1/92-9/96 PM_{13} - 22.7 (10.8) Rome - No PM_{10} Stockholm - 3/94-12/96 15.5 (7.2)	Examined the association between measures of PM to include PM_{10} and hospital admissions for cardiac causes in eight European cities with a combined population of 38 million. Examined age factors and ischemic heart disease and studies also stratified by age using autoregressive Poisson models controlled for long-term trends, season, influenza, epidemics, and meteorology, as well as confounding by other pollutants. In a second regression examined, pooled city-specific results for sources of heterogeneity.	Pooled results were reported for the cardiac admissions results in table format. City-specific and pooled results were depicted in figures only. Found a significant effect of PM_{10} and black smoke on admissions for cardiac causes (all ages) and cardiac causes and ischemic heart disease for people over 65 years with the impact of PM_{10} per unit of pollution being half that found in the United States. PM_{10} did not seem to be confounded by O_3 or SO_2. The effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. There was little evidence of an impact of particles on hospital admissions for ischemic heart disease for people below 65 years or stroke for people over 65 years. The authors state results were consistent with a role for traffic exhaust/diesel in Europe.	For a 10 $\mu g/m^3$ increase in PM_{10} Cardiac admissions/all ages 0.5% (0.2, 0.8) Cardiac admissions/over 65 years 0.7% (0.4, 1.0) Ischemic heart disease/over 65 years 0.8% (0.3, 1.2) For cardiac admissions for people over 65 years: All the city-specific estimates were positive with London, Milan, and Stockholm significant at the 5% level.
Atkinson et al. (1999a) Greater London, England 1992-1994 Pollutant: mean, median, 90-10 percentile range: PM_{10} ($\mu g/m^3$): 28.5, 24.8, 30.7 Black Smoke ($\mu g/m^3$): 12.7, 10.8, 16.1	Daily emergency hospital admissions for total cardiovascular diseases, CVD (ICD9 codes 390-459), and ischemic heart disease, IHD (ICD9 410-414), for all ages, for persons less than 65, and for persons 65 and older. Mean daily admissions for CVD: 172.5 all ages, 54.5 <65, 117.8 ≥65; for IHD: 24.5 <65, 37.6 ≥65. Covariates: NO_2, O_3, SO_2, CO, temperature, relative humidity. Poisson regression using APHEA methodology; sine and cosine functions for seasonal control; day of week dummy variables. Lags of 0-3, as well as corresponding multi-day averages ending on lag 0, were considered.	In single-pollutant models, both PM metrics showed positive associations with both CVD and IHD admissions across age groups. In Two-pollutant models, the BS effect, but not the PM_{10} effect, was robust. No quantitative results provided for two-pollutant models. Study does not support a PM_{10} effect independent of co-pollutants.	Effects computed for 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ BS PM_{10} 0 d. All ages: CVD: 3.2 (0.9, 5.5) 0–64 yr: CVD: 5.6 (2.0, 9.4) IHD: 6.8 (1.3, 12.7) 65+ yr: CVD: 2.5 (−0.2, 5.3) IHD: 5.0 (0.8, 9.3) Black Smoke 0 d. All ages: CVD: 2.95 (1.00, 4.94) 0–64 yr: CVD: 3.12 (0.05, 6.29) IHD: 2.78 (−1.88, 7.63) 65+ yr: CVD: 4.24 (1.89, 6.64) IHD (lag 3): 4.57 (0.86, 8.42)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh, Scotland 1981-1995 (BS and SO_2) 1992-1995 (PM_{10}, NO_2, O_3, CO) Means for long and short series: BS: 12.3, 8.7 PM_{10}: NA, 20.7	Daily emergency hospital admissions for cardiovascular disease (ICD9 codes 410-414, 426-429, 434-440) for persons less than 65 years and for persons 65 or older. Separate analyses presented for long (1981-1995) and short (1992-1995) series. Mean hospital admissions for long and short series: <65, 3.5, 3.4; 65+, 8.0, 8.7. Covariates: SO_2, NO_2, O_3, CO, wind speed, temperature, rainfall. PM_{10} measured by TEOM. Stats: Poisson log-linear regression; trend and seasons controlled by monthly dummy variables over entire series; day of week dummy variables; min daily temperature modeled using octile dummies. Pollutants expressed as cumulative lag 1-3 day moving avg.	In long series, neither BS nor NO_2 were associated with CVD admissions in either age group. In the short series, only 3-day moving average PM_{10} was positively and significantly associated with CVD admissions in single-pollutant models, and only for persons 65 or older. BS, SO_2, and CO also showed positive associations in this subset, but were not significant at the 0.05 level. The PM_{10} effect remained largely unchanged when all other pollutants were added to the model, however quantitative results were not given. Results appear to show an effect of PM_{10} independent of co-pollutants.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10} and 25 $\mu g/m^3$ change in BS. Long series: BS, 1–3 d. avg. <65: −0.5 (−5.4, 4.6) 65+: −0.5 (−3.8, 2.9) Short series: BS, 1–3 d. avg. <65: −9.5 (−24.6, 8.0) 65+: 5.8 (−4.9, 17.8) PM_{10}, 1–3 d. avg. <65: 2.0 (−12.5, 19.0) 65+: 12.4 (4.6, 20.9)
Wordley et al. (1997) Birmingham, UK 4/1/92-3/31/94 mean, min, max: PM_{10} ($\mu g/m^3$): 26, 3, 131	Daily hospital admissions for acute ischemic heart disease (ICD9 codes 410-429) for all ages. Mean hospitalizations: 25.6/day. Covariates: temperature and relative humidity. Stats: Linear regression with day of week and monthly dummy variables, linear trend term. Lags of 0-3 considered, as well as the mean of lags 0-2.	No statistically significant effects observed for PM_{10} on ischemic heart disease admissions for any lag. Note that PM_{10} was associated with respiratory admissions and with cardiovascular mortality in the same study (results not shown here).	% change (95% CI) per 50 $\mu g/m^3$ change PM_{10} IHD admissions: PM_{10} 0-d lag: 1.4% (−4.4, 7.2) PM_{10} 1-d lag: −1.3% (−7.1, 4.4)
Díaz et al. (1999) Madrid, Spain 1994-1996 TSP by beta attenuation Summary statistics not given.	Daily emergency hospital admissions for all cardiovascular causes (ICD9 codes 390-459) for the Gregorio Maranon University Teaching Hospital. Mean admissions: 9.8/day. Covariates: SO_2, NO_2, O_3, temperature, pressure, relative humidity, excess sunlight. Stats: Box-Jenkins time-series methods used to remove autocorrelations, followed by cross-correlation analysis; sine and cosine terms for seasonality; details unclear.	No significant effects of TSP on CVD reported.	No quantitative results presented for PM.

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Australia			

Morgan et al. (1998) Sydney, Australia 1990-1994
 	
 mean, median, IQR, 90-10 percentile range: Daily avg. bscat/10^4m: 0.32, 0.26, 0.23, 0.48 Daily max 1-hr bscat/10^4m: 0.76, 0.57, 60, 1.23
	Daily hospital admissions for heart disease (ICD9 codes 410, 413, 427, 428) for all ages, and separately for persons less than 65 and persons 65 or greater. Mean daily admissions: all ages, 47.2; <65, 15.4; 65+, 31.8. PM measured by nephelometry (i.e., light scattering), which is closely associated with $PM_{2.5}$. Authors give conversion for Sydney as $PM_{2.5} = 30 \times$ bscat. Covariates: O_3, NO_2, temperature, dewpoint temperature. Stats: Poisson regression; trend and seasons controlled with linear time trend and monthly dummies; temperature and dewpoint controlled with dummies for eight levels of each variable; day of week and holiday dummies. Single and cumulative lags from 0-2 considered. Both single and multi-pollutant models were examined.	In single-pollutant models, NO_2 was strongly associated with heart disease admissions in all age groups. PM was more weakly, but still significantly associated with admissions for all ages and for persons 65+. The NO_2 association in the 65+ age group was unchanged in the multi-pollutant model, whereas the PM effect disappeared when NO_2 and O_3 were added to the model.. These results suggest that PM is not robustly associated with heart disease admissions when NO_2 is included, similar to the sensitivity of PM to CO in other studies.	Percent Excess Risk (95% CI): Effects computed for 25 μg/m^3 $PM_{2.5}$ (converted from bscat).
			
			 24-hr avg. $PM_{2.5}$ 0 d.
			   <65: 1.8 (−2.9, 6.7)
			   65+: 4.9 (1.6, 8.4)
			   All: 3.9 (1.1, 6.8)
			
			 24-hr $PM_{2.5}$, 0 d w. NO_2 and O_3.
			   65+: 0.12 (−1.3, 1.6)
			
			 1-hr $PM_{2.5}$, 0 d.
			   <65: 0.19 (−1.6, 2.0)
			   65+: 1.8 (0.5, 3.2)
			   All: 1.3 (0.3, 2.3)

Asia			

Wong et al. (1999) Hong Kong 1994-1995 median, IQR for PM_{10} (μg/m^3): 45.0, 34.8	Daily emergency hospital admissions for cardiovascular diseases, CVD (ICD9 codes 410-417, 420-438, 440-444), heart failure, HF (ICD9 428), and ischemic heart disease, IHD (ICD9 410-414) among all ages and in the age categories 5-64, and 65+. Median daily CVD admissions for all ages: 101. Covariates: NO_2, O_3, SO_2, temperature, relative humidity. PM_{10} measured by TEOM. Stats: Poisson regression using the APHEA protocol; linear and quadratic control of trends; sine and cosine control for seasonality; holiday and day of week dummies; autoregressive terms. Single and cumulative lags from 0-5 days considered.	In single-pollutant models, PM_{10}, NO_2, SO_2, and O_3 all significantly associated with CVD admissions for all ages and for those 65+. No multi-pollutant risk coefficients were presented; however, the PM_{10} effect was larger when O_3 was elevated (i.e., above median). A much larger PM_{10} effect was observed for HF than for CVD or IHD. These results confirm the presence of PM_{10} associations with cardiovascular admissions in single-pollutant models, but do not address the independent role of PM_{10}.	Percent Excess Risk (95% CI): Effects computed for 50 μg/m^3 change in PM_{10}.
			
			 PM_{10}, 0−2 d. avg.
			
			 CVD:
			   5−64: 2.5 (−1.5, 6.7)
			   65+: 4.1 (1.3, 6.9)
			   All: 3.0 (0.8, 5.4)
			
			 HF (PM_{10}, 0-3 d ave.):
			   All: 26.4 (17.1, 36.4)
			
			 IHD (PM_{10}, 0-3 d ave.):
			   All: 3.5 (−0.5, 7.7)

Appendix 8B.2. PM-Respiratory Hospitalization Studies

TABLE 8B-2. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation. Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Samet et al, (2000a,b) Study Period.: 84- 95 14 U.S. Cities: Birmingham, Boulder, Canton, Chicago, Col. Springs, Detroit, Minn./St. Paul, Nashville, New Haven, Pittsburgh, Provo/Orem, Seattle, Spokane, Youngstown. Mean pop. aged 65+ yr per city =143,000 PM_{10} mean = 32.9 $\mu g/m^3$ PM_{10} IQR = NR	Hospital admissions for adults 65+ yrs. for CVD (mean=22.1/day/city), COPD (mean=2.0/day/city), and Pneumonia (mean=5.6/day/city) related to PM_{10}, SO_2, O_3, NO_2, and CO. City-specific Poisson models used with adjustment for season, mean temperature (T) and relative humidity (RH) (but not their interaction), as well as barometric pressure (BP) using LOESS smoothers (span usually 0.5). Indicators for day-of-week and autoregressive terms also included.	PM_{10} positively associated with all three hospital admission categories, but city specific results ranged widely, with less variation for outcomes with higher daily counts. PM_{10} effect estimates not found to vary with co-pollutant correlation, indicating that results appear quite stable when controlling for confounding by gaseous pollutants. Analyses found little evidence that key socioeconomic factors such as poverty or race are modifiers, but it is noted that baseline risks may differ, yielding differing impacts for a given RR.	PM_{10} = 50 $\mu g/m^3$ COPD HA's for Adults 65+ yrs. Lag 0 ER = 7.4% (CI: 5.1, 9.8) Lag 1 ER = 7.5% (CI: 5.3, 9.8) 2 day mean (lag0,lag1) ER = 10.3% (CI: 7.7, 13) Pneumonia HA's for Adults 65+ yrs. Lag 0 ER =8.1% (CI: 6.5, 9.7) Lag 1 ER = 6.7% (CI: 5.3, 8.2) 2 day mean (lag0, lag1) = 10.3% (CI: 8.5, 12.1)
Zanobetti et al. (2000b) 10 U.S. Cities	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular and respiratory disease in persons aged ≥65 yr. Covariates: SO_2, O_3, CO, temperature, relative humidity, barometric pressure. In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 d considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50$\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. Suggests association between PM_{10} and total respiratory hospital admissions among the elderly.	Percent excess respiratory risk (95% CI) per 50 $\mu g/m^3$ PM_{10} increase: COPD (0-1 d lag) = 10.6 (7.9, 13.4) COPD (unconstrained dist. lag) = 13.4 (9.4, 17.4) Pneumonia (0-1 d lag) = 8.1 (6.5, 9.7) Pneumonia (unconstrained dist. lag) = 10.1 (7.7, 12.6)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Jamason et al. (1997) New York City, NY (82 - 92) Population = NR PM_{10} mean = 38.6 $\mu g/m^3$	Weather/asthma relationships examined using a synoptic climatological multivariate methodology. Procedure relates homogenous air masses to daily counts of overnight asthma hospital admission.	Air pollution reported to have little role in asthma variations during fall and winter. During spring and summer, however, the high risk categories are associated with high concentration of various pollutants (i.e., PM_{10}, SO_2, NO_2, O_3).	NR
Chen et al. (2000) Reno-Sparks, NV (90 - 94) Population = 307,000 B-Gauge PM_{10} mean=36.5 $\mu g/m^3$ PM_{10} IQR = 18.3-44.9 $\mu g/m^3$ PM_{10} maximum = 201.3 $\mu g/m^3$	Log of COPD (mean=1.72/day) and gastroenteritis (control) admissions from 3 hospitals analyzed using GAM regression, adjusting for effects of day-of-week, seasons, Weather effects (T, WS), and long-wave effects. No co-pollutants considered.	PM_{10} positively associated with COPD admissions, but no association with gastroenteritis (GE) diseases, indicating biologically plausible specificity of the PM_{10}-health effects association. Association remained even after excluding days with PM_{10} above 150 $\mu g/m^3$.	COPD All age Admissions 50 $\mu g/m^3$ IQR PM_{10} (single pollutant): ER = 9.4% (CI: 2.2, 17.1)
Gwynn et al. (2000) Buffalo, NY (5/88-10/90) PM_{10} mn./max. = 24.1/90.8 $\mu g/m^3$ PM_{10} IQR = 14.8-29.2 $\mu g/m^3$ $SO_4^=$ mn./max. = 2.4/3.9 $\mu g/m^3$ $SO_4^=$ IQR = 23.5 – 7.5 $\mu g/m^3$ H^+ mn/max = 36.4/382 nmol/m^3 H^+ IQR = 15.7-42.2 nmol/m^3 CoH mn/max = 0.2/0.9 10^{-3} ft. CoH IQR = 0.1-0.3	Air pollutant-health effect associations with total, respiratory, and circulatory hospital admissions and mortality examined using Poisson methods controlling for weather, seasonality, long-wave effects, day of week, holidays,	Strongest associations found between $SO_4^=$ and respiratory hospital admissions, while secondary aerosol H^+ and $SO_4^=$ demonstrated the most coherent associations across both respiratory hospital admissions and mortality. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. CoH weakness in associations may reflect higher toxicity by acidic sulfur containing secondary particles versus carbonaceous primary particles.	Respiratory Hospital Admissions(all ages) PM Index (using standardized conc. increment) -Single Pollutant Models For PM_{10} = 50$\mu g/m^3$; SO_4 = 15$\mu g/m^3$; H^+ = 75nmoles/m^3;COH = 0.5 units/1000ft PM_{10}(lag 0) ER = 11% (CI: 4.0, 18) $SO_4^=$(lag 0) ER = 8.2% (CI: 4.1, 12.4) H^+(lag 0) ER = 6% (CI: 2.8, 9.3) CoH(lag0) ER = 3% (CI: −1.2, 7.4)
Gwynn et al. (2001) New York City, NY 1988, 89, 90 PM_{10} 37.4 $\mu g/m^3$ mean	Respiratory hospital admissions, race specific for PM_{10}, H^+, O_3, $SO_4^=$. Regression model used to model daily variation in respiratory hospital admissions, day-week, seasonal, and weather aspects addressed in modeling.	Greatest difference between the white and non-white subgroups was observed for O_3. However, within race analyses by insurable coverage suggested that most of the higher effects of air pollution found for minorities were related to socio-economic studies.	PM_{10} (max-min) increment 1 day lag white 1.027 (0.971-1.074) non-white (1.027 (0.988-1.069)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Jacobs et al. (1997) Butte County, CA (83 - 92) Population = 182,000 PM_{10} mean = 34.3 $\mu g/m^3$ PM_{10} min/max = 6.6 / 636 $\mu g/m^3$ CoH mean = 2.36 per 1000 lin. ft. CoH min/max = 0 / 16.5	Association between daily asthma HA's (mean = 0.65/day) and rice burning using Poisson model with a linear term for temperature, and indicator variables for season and yearly population. Co-pollutants were O_3 and CO. PM_{10} estimated for 5 of every 6 days from CoH.	Increases in rice straw burn acreage found to correlate with asthma HA's over time. All air quality parameters gave small positive elevations in RR. PM_{10} showed the largest increase in admission risk.	Asthma HA's (all ages) For an increase of 50 $\mu g/m^3$ PM_{10}: ER = 6.11% (not statistically significant)
Linn et al. (2000) Los Angeles, CA (92 - 95) Population = NR PM_{10} mean = 45.5 $\mu g/m^3$ PM_{10} Min/Max = 5/132 $\mu g/m^3$	Pulmonary hospital admissions (HA's) (mean=74/day) related to CO, NO_2, PM_{10}, and O_3 in Los Angeles using Poisson model with long-wave, day of week, holidays, and weather controls.	PM_{10} positively associated with pulmonary admissions year-round, especially in winter. No association with cerebro-vascular or abdominal control diseases. However, use of linear temperature, and with no RH interaction, may have biased effect estimates downwards for pollutants here most linearly related to temperature (i.e., O_3 and PM_{10}).	Pulmonary HA's (>29 yrs.) PM_{10} = 50 $\mu g/m^3$ (Lag 0)ER = 3.3% (CI: 1.7, 5)
Moolgavkar et al. (1997) Minneapolis-St. Paul 86 - 91 Population.= NR Birmingham, AL '86-'91 Population. = NR PM_{10} mean = 34 $\mu g/m^3$ (M-SP) PM_{10} IQR =22-41 $\mu g/m^3$ (M-SP) PM_{10} mean =43.4 $\mu g/m^3$ (Birm) PM_{10} IQR =26-56 $\mu g/m^3$ (Birm)	Investigated associations between air pollution (PM_{10}, SO_2, NO_2 O_3, and CO) and hospital admissions for COPD (mean/day=2.9 in M-SP; 2.3 in Birm) and pneumonia (mean=7.6 in M-SP; 6.0 in Birm) among older adults (>64 yrs.). Poisson GAM's used, controlling for day-of-week, season, LOESS of temperature (but neither RH effects nor T-RH interaction considered).	In the M-SP area, PM_{10} significantly and positively associated with total daily COPD and pneumonia admissions among elderly, even after simultaneous inclusion of O_3. When four pollutants included in the model (PM_{10}, SO_2, O_3, NO_2), all pollutants remained positively associated. In Birm., neither PM_{10} nor O_3 showed consistent associations across lags. The lower power (fewer counts) and lack of T-RH interaction weather modeling in this Southern city vs. M-SP may have contributed to the differences seen between cities.	COPD + Pneumonia Admissions (>64yrs.) In M-SP, For PM_{10} = 50 $\mu g/m^3$ (max lg) ER(lg 1) = 8.7% (CI: 4.6, 13) With O_3 included simultaneously: ER(lg1)= 6.9% (95 CI: 2.7, 11.3) In Birm, For PM_{10}=50 $\mu g/m^3$ (max lg.) ER(lg 0) = 1.5% (CI: −1.5, 4.6) With O_3 included simultaneously: ER(lg0) = 3.2% (CI: −0.7, 7.2)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Nauenberg and Basu (1999) Los Angeles (91 - 94) Wet Season = 11/1-3/1 Dry Season = 5/1-8/15 Population .= 2.36 Million PM_{10} Mean = 44.81 $\mu g/m^3$ PM_{10} SE = 17.23 $\mu g/m^3$	The effect of insurance status on the association between asthma-related hospital admissions and exposure to PM_{10} and O_3 analyzed, using regression techniques with same day and 8-day weighted moving average levels, after removing trends using Fourier series. Compared results during wet season for all asthma HA's (mean = 8.7/d), for the uninsured (mean=0.77/d), for MediCal (poor) patients (mean = 4.36/d), and for those with other private health or government insurance (mean = 3.62/d).	No associations found between asthma admissions and O_3. No O_3 or PM_{10} associations found in dry season. PM_{10} averaged over eight days associated with increase in asthma admissions, with even stronger increase among MediCal asthma admissions in wet season. The authors conclude that low income is useful predictor of increased asthma exacerbations associated with air pollution. Non-respiratory HA's showed no such association with PM_{10}.	<u>All Age Asthma HA's</u> PM_{10} = 50 $\mu g/m^3$, no co-pollutant, during wet season (Jan. 1 - Mar. 1): <u>All Asthma Hospital Admissions</u> 0-d lag PM_{10} ER = 16.2 (CI: 2.0, 30) 8-d avg. PM_{10} ER = 20.0 (CI: 5.3, 35) <u>MediCal Asthma Hospital Admissions</u> 8-d avg. PM_{10} ER = 13.7 (3.9, 23.4) <u>Other Insurance Asthma HA's</u> 8-d avg. PM_{10} ER = 6.2 (−3.6, 16.1)
Schwartz et al. (1996b) Cleveland (Cayahoga County), Ohio (88 - 90) PM_{10} mean = 43 $\mu g/m^3$ PM_{10} IQR = 26 – 56 $\mu g/m^3$	Review paper including an example drawn from respiratory hospital admissions of adults aged 65 yr and older (mean = 22/day) in Cleveland, OH. Categorical variables for weather and sinusoidal terms for filtering season employed.	Hospital admissions for respiratory illness of persons aged 65 yr and over in Cleveland strongly associated with PM_{10} and O_3, and marginally associated with SO_2 after control for season, weather, and day of the week effects.	<u>Respiratory HA's for persons 65+ years</u> 50 $\mu g/m^3$ PM_{10} ER = 5.8% (CI: 0.5, 11.4)
Zanobetti, et al. (2000a) Study Period: 86 - 94 Chicago (Cook Count), IL Population = 633,000 aged 65+ PM_{10} mean = 33.6 $\mu g/m^3$ PM_{10} range = 2.2, 157.3 $\mu g/m^3$	Analyzed HA's for older adults (65 + yr) for COPD (mean = 7.8/d), pneumonia (mean = 25.5/d), and CVD, using Poisson regression controlling for temperature, dew point, barometric pressure, day of week, long wave cycles and autocorrelation, to evaluate whether previous admission or secondary diagnosis for associated conditions increased risk from air pollution. Effect modification by race, age, and sex also evaluated.	Air pollution- associated CVD HA's were nearly doubled for those with concurrent respiratory infections (RI) vs. those without concurrent RI. For COPD and pneumonia admissions, diagnosis of conduction disorders or dysrhythmias (Dyshr.) increased PM_{10} RR estimate. The PM_{10} RR effect size did not vary significantly by sex, age, or race, but baseline risks across these groups differ markedly, making such sub-population RR inter-comparisons difficult to interpret.	PM_{10} = 50 $\mu g/m^3$(average of lags 0,1) <u>COPD (adults 65+ yrs.)</u> W/o prior RI. ER = 8.8% (CI: 3.3, 14.6) With prior RI ER = 17.1% (CI: −6.7, 46.9) <u>COPD (adults 65+ yrs.)</u> W/o concurrent Dys. ER = 7.2% (CI: 1.3, 13.5) With concurrent Dys. ER = 16.5%(CI: 3.2, 31.5) <u>Pneumonia (adults 65+ yrs.)</u> W/o pr. Asthma ER = 11% (CI: 7.7, 14.3) With pr. Asthma ER = 22.8% (CI: 5.1, 43.6) <u>Pneumonia (adults 65+ yrs.)</u> W/o pr. Dyshr. ER = 10.4% (CI: 6.9, 14) With pr. Dyshr. ER = 18.8% (CI: 6.3, 32.7)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants

United States (cont'd)

Lippmann et al. (2000) Detroit, MI ('92-'94) Population = 2.1 million PM_{10} Mean = 31 $\mu g/m^3$ (IQR= 19, 38 $\mu g/m^3$; max=105$\mu g/m^3$) $PM_{2.5}$ Mean = 18 $\mu g/m^3$ (IQR= 10, 21 $\mu g/m^3$; max=86 $\mu g/m^3$) $PM_{10-2.5}$ Mean = 12 $\mu g/m^3$ (IQR= 8, 17 $\mu g/m^3$; max=50 $\mu g/m^3$) SO_4^- Mean = 5 $\mu g/m^3$ (IQR=1.8, 6.3 $\mu g/m^3$; max=34.5 $\mu g/m^3$) H^+ Mean = 8.8 nmol/m^3 = 0.4 $\mu g/m^3$ (IQR=0, 7nmol/m^3;max=279)	Respiratory (COPD and Pneumonia) HA's for persons 65 + yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For respiratory HA's, all PM metrics yielded RR's estimates >1, and all were significantly associated in single pollutant models for pneumonia. For COPD, all PM metrics gave RR's >1, with H^+ being associated most significantly, even after the addition of O_3 to the regression. Adding gaseous pollutants had negligible effects on the various PM metric RR estimates. The most consistent effect of adding co-pollutants was to widen the confidence bands on the PM metric RR estimates: a common statistical artifact of correlated predictors. Despite usually non-detectable levels, H^+ had strong association with respiratory admissions on the few days it was present. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per $\mu g/m^3$ in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity is usually not present.	Pneumonia HA's for 65+ yrs. No co-pollutant: PM_{10} (50 $\mu g/m^3$) 1d lag ER = 22% (CI: 8.3, 36) $PM_{2.5}$ (25 $\mu g/m^3$) 1d lag: ER = 13% (CI: 3.7, 22) $PM_{2.5-10}$ (25 $\mu g/m^3$) 1d lag: ER = 12% (CI: 0.8, 24) H^+ (75 nmol/m^3) 3d lag: ER = 12% (CI: 0.8, 23) O_3 co-pollutant (lag 3) also in model: PM_{10} (50 $\mu g/m^3$) 1d lag, ER = 24% (CI: 8.2, 43) $PM_{2.5}$ (25 $\mu g/m^3$) 1d lag: ER = 12% (CI: 1.7, 23) $PM_{2.5-10}$ (25 $\mu g/m^3$) 1d lag: ER = 14% (CI: 0.0, 29) H^+ (75 nmol/m^3) 3d lag: ER = 11% (CI: −0.9, 24) COPD Hospital Admissions for 65+ yrs. No co-pollutant: PM_{10} (50 $\mu g/m^3$) 3d lag ER = 9.6% (CI: −5.1, 27) $PM_{2.5}$ (25 $\mu g/m^3$) 3d lag: ER = 5.5% (CI: −4.7, 17) $PM_{2.5-10}$ (25 $\mu g/m^3$) 3d lag: ER = 9.3% (CI: −4.4, 25) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: 0.0, 28) O_3 co-pollutant (lag 3) also in model: PM_{10} (50 $\mu g/m^3$) 3d lag, ER = 1.0% (-15, 20) $PM_{2.5}$ (25 $\mu g/m^3$) 3d lag: ER = 2.8% (CI: −9.2, 16) $PM_{2.5-10}$ (25 $\mu g/m^3$) 3d lag: ER = 0.3% (CI: −14, 18) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: −0.6, 28)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lumley and Heagerty (1999) Seattle (King Cty.), WA (87-94) Population = NR PM_1 daily mean = NR PM_{1-10} daily mean = NR From Sheppard et al, 1999: PM_{10} mean = 31.5 $\mu g/m^3$ PM_{10} IQR = 19-39 $\mu g/m^3$ $PM_{2.5}$ mean = 16.7 $\mu g/m^3$ $PM_{2.5}$ IQR = 8-21 $\mu g/m^3$	Estimating equations based on marginal generalized linear models applied to respiratory HA's for persons <65 yrs. of age (mean ˜ 8/day) using class of variance estimators based upon weighted empirical variance of the estimating functions. Poisson regression used to fit a marginal model for the log of admissions with linear temperature, day of week, time trend, and dummy season variables. No co-pollutants considered.	PM_1 at lag 1 day associated with respiratory HA's in children and younger adults (<65), but not PM_{10}-$_1$, suggesting a dominant role by the submicron particles in $PM_{2.5}$–asthma HA associations reported by Sheppard et al. (1999). 0-day lag PM_1 and 0 and 1 day lag PM_{1-10} had RR near 1 and clearly non-significant. Authors note that model residuals correlated at r=0.2, suggesting the need for further long-wave controls in the model (e.g., inclusion of the LOESS of HA's).	Respiratory HA's for persons <65 yrs. old PM_1 = 25 $\mu g/m^3$, no co-pollutant: 1-d lag ER = 5.9 (1.1, 11.0)

Moolgavkar et al. (2000)
King County, WA (87 - 95)
Population = NR
PM_{10} mean = 30.0 $\mu g/m^3$
PM_{10} IQR =18.9-37.3 $\mu g/m^3$
$PM_{2.5}$ mean =18.1 $\mu g/m^3$
$PM_{2.5}$ IQR =10-23 $\mu g/m^3$
	Association between air pollution and hospital admissions (HA's) for COPD (all age mean=7.75/day; 0-19 yrs. mean=2.33/day) investigated using Poisson GAM's controlling for day-of-week, season, and LOESS of temperature. Co-pollutants addressed: O_3, SO_2, CO, and pollens. $PM_{2.5}$ only had one monitoring site versus multiple sites averaged for other pollutants.	Of the PM metrics, PM_{10} showed the most consistent associations across lags (0-4 d). $PM_{2.5}$ yielded the strongest positive PM metric association at lag3 days, but gave a negative association at lag4 days. That $PM_{2.5}$ only had one monitoring site may have contributed to its effect estimate variability. Residual autocorrelations (not reported) may also be a factor. Adding gaseous co-pollutants or pollens decreased the $PM_{2.5}$ effect estimate less than PM_{10}. Analyses indicated that asthma HA's among the young were driving the overall COPD-air pollution associations.	COPD HA's all ages (no co-pollutant)
			PM_{10} (50 $\mu g/m^3$, lag 2)
			    ER = 5.1% (CI: 0, 10.4)
			$PM_{2.5}$ (25 $\mu g/m^3$, lag 3)
			    ER = 6.4% (CI: 0.9, 12.1)
			
			COPD HA's all ages (CO as co-pollutant)
			PM_{10} (50 $\mu g/m^3$, lag 2)
			    ER = 2.5% (CI: −2.5, 7.8)
			$PM_{2.5}$ (25 $\mu g/m^3$, lag 3)
			    ER = 5.6% (CI: 0.2, 11.3)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants

United States (cont'd)

Moolgavkar (2000a) Study Period: 1987-1995 Chicago (Cook County), IL Population = NR PM_{10} median = 35 $\mu g/m^3$ PM_{10} IQR = 25-47 $\mu g/m^3$ Los Angeles (LA County), CA Population = NR PM_{10} median = 44 $\mu g/m^3$ PM_{10} IQR = 33-59 $\mu g/m^3$ $PM_{2.5}$ median = 22 $\mu g/m^3$ $PM_{2.5}$ IQR = 15-31 $\mu g/m^3$ Phoenix (Maricopa County), AZ Population = NR PM_{10} median = 41 $\mu g/m^3$ PM_{10} IQR = 32-51 $\mu g/m^3$	Investigated associations between air pollution (PM_{10}, O_3, SO_2, NO_2, and CO) and COPD Hospital Admissions (HA's). $PM_{2.5}$ also analyzed in Los Angeles. HA's for adults >65 yr.: median=12/day in Chicago, =4/d in Phoenix; =20/d in LA. In LA, analyses also conducted for children 0-19 yr. (med.=17/d) and adults 20-64 (med.=24/d). Poisson GAM's used controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. PM data available only every 6th day (except for daily PM_{10} in Chicago), vs. every day for gases. Power likely differs across pollutants, but number of sites and monitoring days not presented. Two pollutant models forced to have same lag for both pollutants. Autocorrelations or intercorrelations of pollutant coefficients not presented or discussed.	For >64 adults, CO, NO_2 and O_3 (in summer) most consistently associated with the HA's. PM effects more variable, especially in Phoenix. Both positive and negative significant associations for PM and other pollutants at different lags suggest possible unaddressed negative autocorrelation. In LA, PM associated with admissions in single pollutant models, but not in two pollutant models. The forcing of simultaneous pollutants to have the same lag (rather than maximum lag), which likely maximizes intercorrelations between pollutant coefficients, may have biased the two pollutant coefficients, but information not presented.. Analysis in 3 age groups in LA yielded similar results. Author concluded that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER Single Pollutant Models: COPD HA's (>64 yrs.) (50 $\mu g/m^3$ PM_{10}): Chicago: Lag 0 ER =2% (CI: −0.2, 4.3) LA: Lag 2 ER = 6.1% (CI: 1.1, 11.3) Phoenix: Lag 0 ER = 6.9% (CI: −4.1, 19.3) LA COPD HA's (50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$) (0-19 yrs.): PM_{10} lg2=10.7%(CI: 4.4, 17.3) (0-19 yrs.): $PM_{2.5}$ lg0=4.3%(CI: −0.1, 8.9) (0-19 yrs.): $PM_{10-2.5}$ lg2=17.1%(CI: 8.9, 25.8) (20-64 yrs.): PM_{10} lg2=6.5%(CI: 1.7, 11.5) (20-64 yrs.): $PM_{2.5}$ lg2=5.6%(CI: 1.9, 9.4) (20-64 yrs.): $PM_{10-2.5}$ lg2=9%(CI: 3, 15.3) (> 64 yrs): PM_{10} lg2 = 6.1% (1.1, 11.3) (> 64 yrs): $PM_{2.5}$ lg2 = 5.1% (0.9, 9.4) (>64 yrs.): $PM_{10-2.5}$ lg3=5.1% (CI: −0.4, 10.9) (>64 yr) 2 Poll. Models (CO = co-poll.) PM_{10}: Lag 2 ER = 0.6% (CI: −5.1, 6.7) $PM_{2.5}$: Lag 2 ER = 2.0% (−2.9, 7.1)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Sheppard et al. (1999) Seattle, WA, Pop. = NR 1987-1994 PM_{10} mean = 31.5 $\mu g/m^3$ PM_{10} IQR = 19-39 $\mu g/m^3$ $PM_{2.5}$ mean = 16.7 $\mu g/m^3$ $PM_{2.5}$ IQR = 8-21 $\mu g/m^3$ $PM_{2.5-10}$ mean = 16.2 $\mu g/m^3$ $PM_{2.5-10}$ IQR = 9-21 $\mu g/m^3$	Daily asthma hospital admissions (HA's) for residents aged <65 (mean=2.7/day) regressed on PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, SO_2, O_3, and CO in a Poisson regression model with control for time trends, seasonal variations, and temperature-related weather effects. Appendicitis HA's analyzed as a control. Except O_3 in winter, missing pollutant measures estimated in a multiple imputation model. Pollutants varied in number of sites available for analysis, CO the most (4) vs. 2 for PM.	Asthma HA's significantly associated with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ mass lagged 1 day, as well as CO. Authors found PM and CO to be jointly associated with asthma admissions. Highest increase in risk in spring and fall. Results conflict with hypothesis that wood smoke (highest in early study years and winter) would be most toxic. Associations of CO with respiratory HA's taken by authors to be an index of incomplete combustion, rather than direct CO biological effect.	Asthma Admissions (ages 0-64) PM_{10} (lag=1day); 50 $\mu g/m^3$ ER = 13.7% (CI: 5.5%, 22.6) $PM_{2.5}$ (lag=1day); 25 $\mu g/m^3$ ER = 8.7% (CI: 3.3%, 14.3) $PM_{2.5-10}$ (lag=1day); 25 $\mu g/m^3$ ER = 11.1% (CI: 2.8%, 20.1)
Friedman et al. (2001) Atlanta, GA Summer 1996/control vs. Olympics PM_{10} decrease for 36.7 $\mu g/m^3$ to 30.8 $\mu g/m^3$	Asthma events in children aged 1 to 16 years were related to pollutant levels contrasting those during the Summer Olympics games during a 17 day period to control periods before and afer the Olympics.	Asthma events were reduced during the Olympic period. A significant reduction in asthma events was associated with ozone concentration. The high correlation between ozone and PM limit the ability to determine which pollutants may have accounted for the reduction in asthma events.	3 day cumulative exposure PM_{10} per 10 $\mu g/m^3$ 1.0 (0.80-2.48)
Zanobetti and Schwartz (2001) Cook County, Illinois 1988-1994 PM_{10}: 33 $\mu g/m^3$ median	Respiratory admissions for lung disease in persons with or without diabetes as a co-morbidity related to PM_{10} measures.	Weak evidence that diabetes modified the risks of PM_{10} induced respiratory hospital admissions while diabetes modified the risk of PM_{10} induced COPD admissions in older people. Found a significant interaction with hospital admissions for heart disease and PM with more than twice the risk in diabetics as in persons without diabetes.	COPD PM_{10} 10 $\mu g/m^3$ with diabetes 2.29 (−0.76-5.44) without diabetes 1.50 (0.42-2.60)
Janssen et al. (2002) 14 U.S. cities 1985-1994 see Samet et al. (2000a,b)	Regression coefficients of the relation between PM_{10} and hospital admissions for respiratory disease from Samet et al. (2000a,b) and prevalence of air conditioning (AC).	Regression coefficients of the relation between ambient PM_{10} and hospital admissions for COPD decreased with increasing percentage of homes with central AC.	—

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants

Canada

Burnett et al. (1997b)
Toronto, Canada (1992-1994),
Pop. = 4 mill.
$PM_{2.5}$ mean = 16.8 $\mu g/m^3$
$PM_{2.5}$ IQR = 8-23 $\mu g/m^3$
$PM_{10-2.5}$ mean = 11.6 $\mu g/m^3$
$PM_{10-2.5}$ IQR = 7-14 $\mu g/m^3$
PM_{10} mean = 28.4 $\mu g/m^3$
PM_{10} IQR = 16-38 $\mu g/m^3$
CoH mean = 0.8 (per 10^3 lin. ft.)
CoH IQR = 0.5-1.1(per 10^3 lin ft)
SO_4 mean = 57.1 nmole/m^3
SO_4 IQR = 14-71 nmole/m^3
H^+ mean = 5 nmole/m^3
H^+ IQR = 0-6 nmole/m^3
	Hospital admissions (HA's) for respiratory diseases (tracheobronchitis, chronic obstructive long disease, asthma, pneumonia) analyzed using Poisson regression (adjusting for long-term temporal trends, seasonal variations, effects of short-term epidemics, day-of-week, ambient temperature and dew point). Daily particle measures: $PM_{2.5}$, coarse particulate mass($PM_{10-2.5}$), PM_{10}, SO_4, H^+, and gaseous pollutants (O_3, NO_2, SO_2, and CO) evaluated.	Positive air pollution-HA associations found, with ozone being pollutant least sensitive to adjustment for co-pollutants. However, even after the simultaneous inclusion of O_3 in the model, the association with the respiratory hospital admissions were still significant for PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, CoH,, SO_4, and H^+.	<u>Respiratory HA's all ages</u>(no co-pollutant)
			PM_{10} (50 $\mu g/m^3$, 4d avg. lag 0)
			  ER = 10.6% (CI: 4.5 - 17.1)
			$PM_{2.5}$ (25 $\mu g/m^3$, 4d avg. lag 1)
			  ER = 8.5% (CI: 3.4, 13.8)
			$PM_{10-2.5}$ (25 $\mu g/m^3$, 5d avg. lag 0)
			  ER = 12.5% (CI: 5.2, 20.0)
			<u>Respiratory HA's all ages</u>(O_3 co-pollutant)
			PM_{10} (50 $\mu g/m^3$, 4d avg. lag 0)
			  ER = 9.6% (CI: 3.5, 15.9)
			$PM_{2.5}$ (25 $\mu g/m^3$, 4d avg., lag 1)
			  ER = 6.2% (1.0, 11.8)
			$PM_{10-2.5}$ (25 $\mu g/m^3$, 5d avg. lag 0)
			  ER = 10.8% (CI: 3.7, 18.1)

Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} ($\mu g/m^3$): 18, 16, 10 CP_{est} ($\mu g/m^3$): 12, 10, 8 $PM_{10\ est}$ ($\mu g/m^3$): 30, 27, 15	Daily hospitalizations for asthma (493, mean 11/day), obstructive lung disease (490-492, 496, mean 5/day), respiratory infection (464, 466, 480-487, 494, mean 13/day) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were <u>estimated</u>, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models. Non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in respiratory outcome. In multi-pollutant models, there were no significant PM associations with any respiratory outcome (results not shown). Use of estimated PM metrics limits the interpretation of pollutant-specific results reported. However, results suggest that a linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when a full range of gaseous pollutants are also modeled.	Percent excess risk (95% CI) per 50 $\mu g/m^3$ PM_{10}; 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$: <u>Asthma</u> $PM_{2.5}$ (0-1-2 d): 6.4 (2.5, 10.6) PM_{10} (0-1 d): 8.9 (3.7, 14.4) $PM_{10-2.5}$ (2-3-4 d): 11.1 (5.8, 16.6) <u>COPD</u> $PM_{2.5}$: 4.8 (−0.2, 10.0) PM_{10}: 6.9 (1.3, 12.8) $PM_{10-2.5}$ (2-3-4 d): 12.8 (4.9, 21.3) <u>Resp. Infection:</u> $PM_{2.5}$: 10.8 (7.2, 14.5) PM_{10}: 14.2 (9.3, 19.3) $PM_{10-2.5}$ (0-1-2 d): 9.3 (4.6, 14.2)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997c) 16 Canadian Cities('81-91) Population=12.6 MM CoH mean=0.64(per 10^3 lin. ft) CoH IQR=0.3-0.8(per 10^3 lin ft)	Air pollution data were compared to respiratory hospital admissions (mean=1.46/million people/day) for 16 cities across Canada. Used a random effects regression model, controlling for long-wave trends, day of week, weather, and city-specific effects.	The 1 day lag of O_3 was positively associated with respiratory admissions in the April to December period, but not in the winter months. Daily maximum 1-hr. CoH from 11 cities and CO also positively associated with HA's, even after controlling for O_3.	Respiratory HA's all ages (with O_3,CO) CoH IQR = 0.5, lag 0: CoH ER = 3.1% (CI: 1.0-4.6%)
Burnett et al. (2001) Toronto, Canada 1980-1994 $PM_{2.5}$: 18 $\mu g/m^3$ $PM_{10-2.5}$: 16.2 $\mu g/m^3$ (both estimated values)	Respiratory admissions in children aged <2 years relates to mean pollution levels. O_3, NO_2, SO_2, and CO (ICD-9: 493 asthma; 466 acute bronchitis; 464.4 croup or pneumonia, 480-486). Time-series analysis adjusted with LOESS.	Summertime urban air pollution, especially ozone, increases the risk that children less than 2 years of age will be hospitalized for respiratory disease.	$PM_{2.5}$ lag 0 15.8% (t=3.29) $PM_{2.5}$ lag 0 with O_3 1.4% (0.24) $PM_{10-2.5}$ lag 1 18.3% (t=3.29) with O_3 4.5% (0.72)
Europe			
Atkinson et al. (1999b) London (92 - 94) Population = 7.2 MM PM_{10} Mean = 28.5 10th-90th IQR = 15.8-46.5 $\mu g/m^3$ BS mean = 12.7 $\mu g/m^3$ 10th-90th IQR = 5.5-21.6 $\mu g/m^3$	All-age respiratory (mean=150.6/day), all-age asthma (38.7/day), COPD plus asthma in adults >64 yr. (22.9/day), and lower respiratory (64.1/day) in adults >64 yr (16.7/day) hospital admissions in London hospitals considered. Counts for ages 0-14, 15-64, and >64 yr also examined. Poisson regression used, controlling for season, day-of-week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	Positive associations found between respiratory-related emergency hospital admissions and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} included simultaneously, size and significance of each was reduced. Authors concluded that SO_2 and PM_{10} are both indicators of the same pollutant mix in this city. SO_2 and PM_{10} analyses by temperature tertile suggest that warm season effects dominate. Overall, results consistent with earlier analyses for London, and comparable with those for North America and Europe.	PM_{10} (50 $\mu g/m^3$), no co-pollutant. All Respiratory Admissions: All age (lag 1d) ER = 4.9% (CI: 1.8, 8.1) 0-14 y (lag 1d) ER = 8.1% (CI: 3.5, 12.9) 15-64y (lag 2d) ER = 6.9% (CI: 2.1, 12.9) 65+ y (lag 3d) ER = 4.9% (CI: 0.8, 9.3) Asthma Admissions: All age (lag 3d) ER = 3.4% (CI: −1.8, 8.9) 0-14 y (lag 3d) ER = 5.4% (CI: −1.2, 12.5) 15-64 y(lag 3d) ER = 9.4% (CI: 1.1, 18.5) 65+ y.(lag 0d) ER = 12% (CI: −1.8, 27.7) COPD & Asthma Admissions (65+yrs.) (lag 3d) ER = 8.6% (CI: 2.6, 15) Lower Respiratory Admissions (65+ yrs.) (lag 3d) ER = 7.6% (CI: 0.9, 14.8)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Wordley et al. (1997) Study Period: 4/92 –3/94 Birmingham, UK Population = NR PM_{10} daily values: Mean = 25.6 $\mu g/m^3$ range = 2.8, 130.9 $\mu g/m^3$ PM_{10} 3 day running. mean: Mean = 25.5 $\mu g/m^3$ range = 7.3, 104.7 $\mu g/m^3$	Relation between PM_{10} and total HA's for respiratory (mean = 21.8/d), asthma (mn.=6.2/d), bronchitis (mn.=2.4/d), pneumonia (mn.=3.4/d), and COPD (mn.=3.2/d) analyzed, using linear regression after adjusting for day of week, month, linear trend, RH, and T (but not T-RH interaction). RR's compared for various thresholds vs. mean risk of HA.	PM_{10} positively associated with all HA's for respiratory, asthma, bronchitis, pneumonia, and COPD. Pneumonia, all respiratory, and asthma HA's also significantly positively associated with the mean of PM_{10} over the past three days, which gave 10 to 20% greater RR's per 10 $\mu g/m^3$, as expected given smaller day to day deviations. Other air pollutants examined but not presented, as "these did not have a significant association with health outcomes independent from that of PM_{10}".	50 $\mu g/m^3$ in PM_{10} <u>All Respiratory HA's (all ages)</u> (lag0d) ER = 12.6% (CI: 5.7, 20) <u>Asthma HA's (all ages)</u> (lag2d) ER = 17.6% (CI: 3, 34.4) <u>Bronchitis HA's (all ages)</u> (lag0d) ER= 32.6% (CI: 4.4, 68.3) <u>Pneumonia HA's (all ages)</u> (lag3d) ER = 31.9% (CI: 15, 51.4) <u>COPD HA's (all ages)</u> (lag1d) ER = 11.5% (CI: −3, 28.2)
Prescott et al. (1998) Edinburgh (10/92-6/95) Population = 0.45 MM PM_{10} mean. =20.7 $\mu g/m^3$ PM_{10} min/max=5/72 $\mu g/m^3$ PM_{10} 90th% - 10th% = 20 $\mu g/m^3$	Poisson log linear regression models used to investigate relation of daily HA's with NO_2, O_3, CO, and PM_{10}. Adjustments made for seasonal and weekday variation, daily T (using 8 dummy variables), and wind speed. Separate analyses for age<65 yr. (mean resp HA = 3.4/day) and age >64 yr. (mean resp HA = 8.7/day), and for subjects with multiple HA's.	The two strongest findings were for cardiovascular HA's of people aged >64, which showed a positive association with PM_{10} as a mean of the 3 previous days. PM_{10} was consistently positively associated with Respiratory HA's in both age groups, with the greatest effect size in those >64, especially among those with >4 HA's during '81-'95. Weak significances likely contributed to by low population size.	Single Pollutant Models PM_{10} = 50 $\mu g/m^3$, mean of lags 1-3 <u>Respiratory HA's (age<65)</u> ER = 1.25 (−12.8, 17.5) <u>Respiratory HA's (age>64)</u> ER = 5.33 (−9.3, 22.3) <u>Respiratory HA's (age>64, >4 HA's)</u> ER = 7.93 (−19.0, 43.7)
McGregor et al. (1999) Birmingham, UK. Population = NR Mean PM_{10} = 30.0 $\mu g/m^3$	A synoptic climatological approach used to investigate linkages between air mass types (weather situations), PM_{10}, and all respiratory hospital admissions (mean= 19.2/day) for the Birmingham area.	Study results show distinct differential responses of respiratory admission rates to the six winter air mass types. Two of three types of air masses associated with above- average admission rates also favor high PM_{10} levels. This is suggestive of possible linkage between weather, air quality, and health.	NR

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hagen et al. (2000) Drammen, Sweden(11/94-12/97) Population = 110,000 PM_{10} mean = 16.8 $\mu g/m^3$ PM_{10} IQR = 9.8-20.9 $\mu g/m^3$	Examined PM_{10}, SO_2, NO_2, VOC's, and O_3 associations with respiratory hospital admissions from one hospital (mean = 2.2/day). Used Poisson GAM controlling for temperature and RH (but not their interaction), long-wave and seasonality, day-of-week, holidays, and influenza epidemics.	As a single pollutant, the PM_{10} effect was of same order of magnitude as reported in other studies. The PM_{10} association decreased when other pollutants were added to the model. However, the VOC's showed the strongest associations.	Respiratory Hospital Admissions(all ages) For IQR=50 $\mu g/m^3$ -Single Pollutant Model: PM_{10} (lag 0) ER = 18.3% (CI: ⁻4.2, 46) -Two Pollutant Model (with O_3): PM_{10} (lag 0) ER = 18.3% (CI: ⁻4.2, 45.4) -Two Pollutant Model (with Benzene): PM_{10} (lag 0) ER = 6.5% (CI:-14 , 31.8)
Dab et al. (1996) Paris, France (87 - 92) Population = 6.1 MM PM_{13} mean = 50.8 $\mu g/m^3$ PM_{13} 5th-95th range = 19.0-137.3 BS mean = 31.9 $\mu g/m^3$ BS 5th-95th Range =11.0-123.3	Daily mortality and general admissions to Paris public hospitals for respiratory causes were considered (means/day: all resp.=79/d, asthma=14/d, COPD=12/d). Time series analysis used linear regression model followed by a Poisson regression. Epidemics of influenza A and B, temperature, RH, holidays, day of week, trend, long-wave variability, and nurses' strike variables included. No two pollutant models considered.	For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association across outcomes. Asthma was significantly correlated with NO_2 levels, but not PM_{13}.	For PM_{13} = 50 $\mu g/m^3$; BS = 25 $\mu g/m^3$; Respiratory HA's (all ages): PM_{13} Lag 0 ER = 2.2% (CI: 0.2, 4.3) BS Lag 0 ER = 1.0% (0.2, 1.8) COPD HA's (all ages): PM_{13} Lag 2 ER = ⁻2.3% (CI: ⁻6.7, 2.2) BS Lag 2 ER = ⁻1.1% (-2.9, 0.6) Asthma HA's (all ages): PM_{13} Lg 2 ER = ⁻1.3% (CI: ⁻4.6, 2.2) BS Lg 0 ER = 1.2% (-0.5, 2.9)
Anderson et al. (1997) Amsterdam(77 - 89) Barcelona (86- 92) London (87 - 91) Milan (80- 89) Paris (87 - 92) Rotterdam (77 - 89) Populations .= 0.7(A), 1.7(B), 7.2(L),1.5(M),6.5(P),0.6(R)MM BS Means = 6, 41, 13, -, 26, 22 TSP Means = 41,155, -, 105, -,41	All-age daily hospital admissions (HA's) for COPD considered in 6 APHEA cities; Mean/day = 1.1(A), 11(B), 20(L), 5(M), 11(P), 1.1(R). Poisson regression controlling for day of week, holidays, seasonal and other cycles, influenza epidemics, temperature, RH, and autocorrelation. Overall multi-city estimates made using inverse variance wts., allowing for inter-city variance.	Ozone gave the most consistent associations across models. Multi-city meta-estimates also indicated associations for BS and TSP. The warm/cold season RR differences were important only for ozone, having a much stronger effect in the warm season. COPD effect sizes found were much smaller than in U.S. studies, possibly due to inclusion of non-emergency admissions or use of less health-relevant PM indices.	BS (25 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 1.7% (0.5, 2.97) TSP (100 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 4.45% (CI: ⁻0.53, 9.67)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Díaz et al. (1999) Madrid (94 - 96) Population = NR TSP mean ≈ 40 $\mu g/m^3$	ARIMA modeling used to analyze emergency respiratory and circulatory admissions (means/day=7.8,7.6) from one teaching hospital. Annual, weekly, and 3 day periodicities controlled, but no time trend included, and temperature crudely fit with v-shaped linear relationship.	Although TSP correlated at zero lag with admissions in winter and year-round, TSP was never significant in ARIMA models; so effect estimates not reported for TSP. Also, found biologically implausible u-shaped relationship for O_3, possibly indicating unaddressed temperature effects.	N/A
Spix et al. (1998) London (L) (87 - 91) Pop. =7.2 Million (MM) BS Mean = 13 $\mu g/m^3$ Amsterdam (A) (77 - 89) Pop. =0.7 MM BS Mean = 6 $\mu g/m3$ TSP mean = 41 $\mu g/m^3$ Rotterdam (R) (77 - 89) Pop. =0.6MM BS Mean = 22 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Paris (P) (87 - 92), Pop.= 6.14 MM BS Mean = 26 $\mu g/m^3$ Milano (M) (80 - 89) Pop. = 1.5 MM TSP Mean =120 ($\mu g/m^3$)	Respiratory (ICD9 460-519) HA's in age groups 15-64 yr and 65 + yrs. related to SO_2, PM (BS or TSP), O_3, and NO_2 in the APHEA study cities using standardized Poisson models with confounder controls for day of week, holidays, seasonal and other cycles, temperature, RH, and autocorrelation. PM lag considered ranged from 0-3 day, but varied from city to city. Quantitative pooling conducted by calculating the weighted means of local regression coefficients using a fixed-effects model when no heterogeneity could be detected; otherwise, a random-effects model employed.	Pollutant associations noted to be stronger in areas where more than one monitoring station was used for assessment of daily exposure. The most consistent finding was an increase of daily HA's for respiratory diseases (adults and elderly) with O_3. The SO_2 daily mean was available in all cities, but SO_2 was not associated consistently with adverse effects. Some significant PM associations were seen, although no conclusion related to an overall particle effect could be drawn. The effect of BS was significantly stronger with high NO_2 levels on the same day, but NO_2 itself was not associated with HA's. Authors concluded that "there was a tendency toward an association of respiratory admissions with BS, but the very limited number of cities prevented final conclusions."	Respiratory Admissions (BS = 25 $\mu g/m^3$) BS (L, A, R, P) 15-64 yrs: 1.4% (0.3, 2.5) 65+ yrs: 1.0% (−0.2, 2.2) TSP (A, R, M) (100 $\mu g/m^3$) 15-64 yrs: 2.0 (−2.1, 6.3) 65+ yrs: 3.2 (−1.2, 7.9) Respiratory HA's BS (L, A, R, P): Warm (25 $\mu g/m^3$) 15-64 yrs: −0.5% (−5.2, 4.4) 65+ yrs: 3.4% (−0.1, 7.1) BS (L, A, R, P): Cold (25 $\mu g/m^3$) 15-64 yrs: 2,0% (0.8, 3.2) 65+ yrs: 0% (−2.2, 2.3) TSP (A, R, M): Warm (100 $\mu g/m^3$) 15-64 yrs: 6.1% (0.1, 12.5) 65+ yrs: 2.0% (−3.9, 8.3) TSP (A, R, M): Cold (100 $\mu g/m^3$) 15-64 yrs: −5.9% (−14.2, 3.2) 65+ yrs: 4.0% (−0.9, 9.2)
Vigotti et al. (1996) Study Period.: 80 - 89 Milan, IT Population = 1.5 MM TSP mean = 139.0 $\mu g/m^3$ TSP IQR = 82.0, 175.7 $\mu g/m^3$	Association between adult respiratory HA's (15-64 yr mean =11.3/day, and 65 + yr mean =8.8/day) and air pollution evaluated, using the APHEA protocol. Poisson regression used with control for weather and long term trend, year, influenza epidemics, and season	Increased risk of respiratory HA was associated with both SO_2 and TSP. The relative risks were similar for both pollutants. There was no modification of the TSP effect by SO_2 level. There was a suggestion of a higher TSP effect on hospital admissions in the cool months.	Young Adult (15-64 yrs.) Resp. HA's 100 $\mu g/m^3$ increase in TSP Lag 2 ER = 5% (CI: 0, 10) Older Adult (65+ yrs.) Resp. HA's 100 $\mu g/m^3$ increase in TSP Lag 1 ER = 5% (CI: −1, 10)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (1998) London (87 - 92) Population = 7.2 MM BS daily mean = 14.6 μg/m^3 BS 25-75th IQR = 24-38	Poisson regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 yr. (mean=19.5/d), 15-64 yr. (mean=13.1/d) and 65 + yr. (mean =2.6/d). Analysis controlled for time trends, seasonal factors, calendar effects, influenza epidemics, RH, temperature, and auto-correlation. Interactions with co-pollutants and aeroallergens tested via 2 pollutant models and models with pollen counts (grass, oak and birch).	Daily hospital admissions for asthma found to have associations with O_3, SO_2, NO_2, and particles (BS), but there was lack of consistency across the age groups in the specific pollutant. BS association was strongest in the 65 + group, especially in winter. Pollens not consistently associated with asthma HA's, sometimes being positive, sometimes negative. Air pollution associations with HA's not explained by airborne pollens in simultaneous regressions, and there was no consistent pollen-pollutant interaction.	Asthma Admissions. BS=25 μg/m^3 BS Lag = 0-3 day average concentration All age ER = 5.98% (0.4, 11.9) <15yr. ER = 2.2% (−4.6, 9.5) 15-64yr ER = 1.2% (−5.3, 8.1) 65+ yr. ER = 22.8% (6.1, 42.5) BS=50 μg/m^3, 2d lag & co-pollutant: Older Adult (>64 yrs.) Asthma Visits: BS alone: ER = 14.6% (2.7, 27.8) &O_3: ER = 20.0% (3.0, 39.8) & NO_2: ER = 7.4% (−8.7, 26.5) SO_2: ER = 11.8% (−2.2, 27.8)
Kontos et al. (1999) Piraeus, Athens GR (87 - 92) Population = NR BS mean =46.5 μg/m^3 BS max =200 μg/m^3	Relation of respiratory HA's for children (0-14 yrs.) (mean = 4.3/day) to BS, SO_2, NO_2, and O_3 evaluated, using a nonparametric stochastic dynamical system approach and frequency domain analyses. Long wave and effects of weather considered, but non-linearity and interactions of T and RH relation with HA's not addressed.	Pollution found to explain significant portion of the HA variance. Of pollutants considered, BS was consistently among most strongly explanatory pollutants across various reported analyses.	NR
Ponce de Leon et al. (1996) London (4/87-2/92) Population = 7.3 million BS mean. =14.6 μg/m^3 BS 5th-95th %=6 - 27 μg/m^3	Poisson regression analysis of daily counts of HA's (means/day: all ages=125.7; Ages 0-14=45.4; Ages 15-64=33.6; Ages 65+=46.7). Effects of trend, season and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity, and autocorrelation addressed. However, temperature modeled as linear, with no RH interaction. Pollution variables were BS, SO_2, O_3, and NO_2, lagged 0-3 days.	O_3 associated with increase in daily HA's, especially in the "warm" season. However, u-shape of the O_3 dose-response suggests that linear temperature control was not adequate. Few significant associations with other pollutants, but these tended to be positive (especially in cold season, Oct-March, and for older individuals for BS).	Respiratory HA's (all ages) Single Pollutant Models For Oct-Mar. BS = 25 μg/m^3 Lag 1 ER = 0.2% (−1.9, 2.3) For Apr-Sep. BS = 25 μg/m^3 Lag 1 ER = -2.7% (−6.0, 0.8) Respiratory HA's (>65) Single Pollutant Models For Oct-Mar. BS = 25 μg/m^3 Lag 2 ER = 1.2% (−2.1, 4.5) For Apr-Sep. BS = 25 μg/m^3 Lag 2 ER = 4.5% (−1.0, 10.4)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Schouten et al. (1996) Amsterdam/Rotterdam (77 - 89) Amsterdam Pop. = 0.69 Million Rotterdam Pop. = 0.58 Million Amsterdam, NE BS mean. =11 $\mu g/m^3$ BS 5th-95th% = 1 - 37 $\mu g/m^3$ Rotterdam, NE BS mean. =26 $\mu g/m^3$ BS 5th-95th %= 6 -61 $\mu g/m^3$	Daily emergency HA's for respiratory diseases (ICD 460-519), COPD (490-492, 494, 496), and asthma (493). The mean HA/d (range) for these were: 6.70 (0-23), 1.74 (0-9) and 1.13 (0-7) respectively in Amsterdam and 4.79 (0-19), 1.57 (0-9), and 0.53 (0-5) in Rotterdam. HA associations with BS, O_3, NO_2, and SO_2 analyzed, using autoregressive Poisson regression allowing for overdispersion and controlling for season, day of week, meteorological factors, and influenza epidemics.	BS did not show any consistent effects in Amsterdam; but in Rotterdam BS was positively related to HA's. Most consistent BS associations in adults >64 yrs. in winter. Positive O_3 association in summer in people aged >64 in Amsterdam and Rotterdam. SO_2 and NO_2 did not show any clear effects. Results not changed in pollutant interaction analyses. The authors concluded short-term air pollution-emergency HA's association is not always consistent at these individual cities' relatively low counts of daily HA's and low levels of air pollution. Analyses for all ages of all the Netherlands gave a strong BS-HA association in winter.	Single Pollutant Models For BS=25 $\mu g/m^3$, 2 day lag For all of the Netherlands: <u>Respiratory HA's (all ages)</u> Winter: ER = 2.0% (−1.5, 5.7) Summer: ER = 2.4% (0.6, 4.3)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Sunyer et al. (1997) Barcelona (86 - 92) Population = NR BS Median: 40 μg/m^3 BS Range: 11-258 (B Helsinki (86 - 92) Population = NR BS Median: - BS Range: - Paris (86 - 92) Population = NR BS Median: 28 μg/m^3 BS Range: 4-186 μg/m^3 London (86 - 92) Population = NR BS Median: 13 μg/m^3 BS Range: 3-95 μg/m^3	Evaluated relations of BS, SO$_2$, NO$_2$, and O$_3$ to daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)]. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities: ED visits in Barcelona; emergency hospital asthma admissions in London and Helsinki, and total asthma admissions in Paris. Estimates from all cities obtained for entire period and also by warm or cold seasons, using Poisson time-series regression, controlling for temperature and RH, viral epidemics, day of week effects, and seasonal and secular trends. Combined associations were estimated using meta-analysis.	Daily admissions for asthma in adults increased significantly with increasing ambient levels of NO$_2$, and positively (but non-significantly) with BS. The association between asthma admissions and pollution varied across cities, likely due to differing asthma outcomes considered. In children, daily admissions increased significantly with SO$_2$ and positively (but non-significantly) with BS and NO$_2$, though the latter only in cold seasons. No association observed in children for O$_3$. Authors concluded that "In addition to particles, NO$_2$ and SO$_2$ (by themselves or as a constituent of a pollution mixture) may be important in asthma exacerbations".	ER per 25 μg/m^3 BS (24 h Average) Asthma Admissions/Visits: <15 yrs.: London ER = 1.5% (lg 0d) Paris ER = 1.5% (lg 2d) Total ER = 1.5% (−1.1, 4.1) 15-64 yrs: Barcelona ER = 1.8% (lg 3d) London ER = 1.7% (lg 0d) Paris ER = 0.6% (lg 0d) Total ER = 1.0% (−0.8, 2.9) Two Pollutant (per 25 μg/m^3 BS) Asthma Admissions (24 h Avg) <15 yrs, (BS & NO$_2$): London ER = 0.6% (lg 0d) Paris ER = 2.9% (lg 2d) Total ER = 1.8% (−0.6, 4.3) <15 yrs, (BS & SO$_2$): London ER = −1.1% (lg 0d) Paris ER = −1.4% (lg 2d) Total ER = −1.3 (−5.0, 2.5) 15-64 yrs, (BS & NO$_2$): Barcelona ER = 1.5% (lg 0d) London ER = −4.7% (lg 0d) Paris ER = −0.7% (lg 1d) Total ER = −0.5% (−5.1, 4.4)
Tenías et al (1998) Study Period.: 94 - 95 Valencia, Spain Hosp. Cachment Pop. =200,000 BS mean = 57.7 μg/m^3 BS IQR = 25.6-47.7 μg/m^3	Associations between adult (14+ yrs.) emergency asthma ED visits to one city hospital (mean =1.0/day) and BS, NO$_2$, O$_3$, SO$_2$ analyzed, using Poisson auto-regressive modeling, controlling for potential confounding weather and time (e.g., seasonal) and trends using the APHEA protocol.	Association with asthma was positive and more consistent for NO$_2$ and O$_3$ than for BS or SO$_2$. Suggests that secondary oxidative-environment pollutants may be more asthma relevant than primary reduction-environment pollutants (e.g., carbonaceous particles). NO$_2$ had greatest effect on BS in co-pollutant models, but BS became significant once 1993 was added, showing power to be a limitation of this study.	Adult Asthma HA's, BS = 25 μg/m^3 For 1993-1995: Lag 0 ER = 10.6% (0.9, 21.1) For 1994-1995: Lag 0 ER = 6.4% (−4.8, 18.8)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (2001) West Midland, England (October 1994-December 1996) Population = 2.3 million PM_{10} mean = 23.3 $\mu g/m^3$ $PM_{2.5}$ mean = 14.5 $\mu g/m^3$ $PM_{10-2.5}$ = 9.0 $\mu g/m^3$ (by subtraction)	Respiratory hospital admissions (mean = 66/day) related to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, SO_4^-, NO_2, O_3, SO_2, CO. Regression with quasilikelihood approach controlling for seasonal patterns, temp, humidity, influenza episodes, day week. Adjusted for residual serial correlation and over-dispersion.	Respiratory admissions (all ages) not associated with any pollutant. Analyses by age revealed some associations to PM_{10} and $PM_{2.5}$ and respiratory admissions in the 0-14 age group. There was a striking seasonal interaction in the cool season versus the warm season. $PM_{10-2.5}$ effects cannot be excluded. Two pollutant models examined particulate measures. $PM_{2.5}$ effects reduced by inclusion of black smoke.	Respiratory HA - lag 0+1 days PM_{10} Increment10-90% (11.4-38.3 $\mu g/m^3$) All ages: 1.5 (−0.7 to 3.6) Ages 0-14: 3.9 (0.6 to 7.4) Ages 15-64: 0.1 (−4.0 to 4.4) Ages ≥65: −1.1 (−4.3 to 2.1) $PM_{2.5}$ (6.0-25.8) All ages: 1.2 (−0.9 to 3.4) Ages 0-14: 3.4 (−0.1 to 7.0) Ages 15-64: −2.1 (−6.4 to 2.4) Ages ≥65: −1.3 (−4.7 to 2.2) $PM_{10-2.5}$ (4.1 to 15.2) All ages: 0.2 (−2.5 to 3.0) Ages 0-14: 4.4 (−0.3 to 9.4) Ages 15-64: −4.9 (−9.9 to 0.4) Ages ≥65: −1.9 (−6.0 to 2.5) COPD (ICD-9 490-492, 494-496) PM_{10} Age ≥65: −1.8 (−6.9 to 3.5) $PM_{2.5}$ Age ≥65: −3.9 (−9.0 to 1.6) $PM_{10-2.5}$ Age ≥65: −1.7 (−8.9 to 5.3) Asthma (ICD- 9-493) (mean lag 0+1) PM_{10} Ages 0-14: 8.3 (1.7 to 15.3) Ages 15-64: −2.3 (−10.0 to 6.1) $PM_{2.5}$ Ages 0-14: 6.0 (−0.9 to 13.4) Ages 15-64: −8.4 (−16.4 to 0.3) $PM_{10-2.5}$ Ages 0-14: 7.1 (−2.1 to 17.2) Ages 15-64: −10.7 (−19.9 to −0.5)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Atkinson et al. (2001) Eight city study: Median/range Barcelona 1/94 – 12/96 PM$_{10}$ 53.3 μg/m^3 (17.1 – 131.7) Birmingham 3/92 – 12/94 PM$_{10}$ 21.5 μg/m^3 (6.5 – 115) London 1/92 – 12/94 PM$_{10}$ 24.9 μg/m^3 (7.2 – 80.4) Milan – No PM$_{10}$ Netherlands 1/92 – 9/95 PM$_{10}$ 33.4 μg/m^3 (11.3 – 130.8) Paris 1/92 – 9/96 PM$_{10}$ 20.1 μg/m^3 (5.8 – 80.9) Rome – No PM$_{10}$ Stockholm 3/94 – 12/96 PM$_{10}$ 13.6 μg/m^3 (4.3 – 43.3)	As part of the APHEA 2 project, association between PM$_{10}$ and daily counts of emergency hospital admissions for Asthma (0-14 and 15-64 yrs), COPD and all-respiratory disease (65+ yrs) controlling for environmental factors and temporal patterns were studied.	This study reports that PM was associated with daily admissions for respiratory disease in a selection of European cities. Average daily ozone levels explained a large proportion of the between-city variability in the size of the particle effect estimates in the over 65 yr age group. In children, the particle effects were confounded with NO$_2$ on a day-to-day basis.	For 10 μg/m^3 increase **Asthma Admission Age 0-14 yrs:** PM$_{10}$ for cities ranged from -0.9% (-2.1, 0.4) to 2.8% (0.8, 4.8) with an overall effect estimate of 1.2% (0.2 – 2.3) **Asthma Admission Age 15-64 yrs:** Overall PM 1.1% (0.3 – 1.8) **Admission of COPD and Asthma Age 65+ years:** Overall PM 1.0% (0.4 – 1.5) **Admission All Respiratory Disease Age 65+ years:** Overall PM 0.9% (0.6 – 1.3)
Thompson et al. (2001) Belfast, Northern Ireland 1/1/93 – 12/31/95. PM$_{10}$ μg/m^3 mean (SD) May – October 24.9 (13.7) November – April 31.9 (24.3)	The rates of acute asthma admission to children's emergency was studied in relation to day-to-day fluctuation of PM$_{10}$ and other pollutants using Poisson regression.	A weak, but significant association between PM10 concentration and asthma emergency-department admissions was seen. After adjusting for multiple pollutants only the benzene level was independently associated with asthma emergency department admission. Benzene was highly correlated to PM$_{10}$, SO$_2$ and NO$_2$ levels.	—
Fusco et al. (2001) Rome, Italy 1995-1997 PM – suspended particles measured	Daily counts of hospital admissions for total respiratory conditions, acute respiratory infection including pneumonia, COPD, and asthma was analyzed in relation to PM measures and gaseous pollutants using generalized additive models controlling for mean temperature, influenza, epidemics, and other factors.	No effect was found for PM. Total respiratory admissions were significantly associated with same-day level of NO$_2$ and CO. There was no indication that the effects of air pollution were present at lags >2 days. Among children, total respiratory and asthma admissions were strongly associated with NO$_2$ and CO. Multipollutant model analysis yielded weaker and more unstable results.	—

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hrubá et al. (2001) (Central Slovakia) (1996) TSP 87 $\mu g/m^3$	Logistic regression modeled TSP exposure and hospital admission for asthma, bronchitis, or pneumonia in children, ages 7-11 years, N=667.	Controlled for age maternal education and other factors. TSP was related to TSP exposure estimates derived from dispersion modeling.	—
Latin America			
Braga et al. (1999) São Paulo, Brazil (92 - 93) Population = NR PM_{10} mean = 66.3 $\mu g/m^3$ PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) to public hospitals serving 40% of the population were regressed (using both Poisson and maximum likelihood methods) on air pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Air pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". Associations ascribed primarily to auto emissions by the authors.	PM_{10} (50 $\mu g/m^3$), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) (0-5day lg avg.) ER = 8.9% (CI: 4.6, 13.4)
Gouveia and Fletcher (2000) Study Period. 92-94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 $\mu g/m^3$ PM_{10} IQR = 42.9-75.5 $\mu g/m^3$ PM_{10}10/90th% =98.1 $\mu g/m^3$ PM_{10} 95th% = 131.6 $\mu g/m^3$	Daily public hospital respiratory disease admissions for children (mean resp. < 5y = 56.1/d; mean pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean pneum.<1y=24.0) and daily levels air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) and were analyzed with Poisson regression. Models adjusted for time trends, seasonal patterns, weekdays, holidays, weather, and serial correlation. PM_{10} measured by Beta-gauge. Private hospitals serving wealthier citizens not in database.	Children's HA's for total respiratory and pneumonia positively associated with O_3, NO_2, and PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with other reports, but smaller RR's. This may be due to higher baseline admission rates in this poor sub-population vs. other studies, but this was not intercompared by the authors.	PM_{10} = 50 $\mu g/m^3$: All Respiratory HA's for children < 5yrs. ER = 2.0% (−0.8, 4.9) Pneumonia HA's for children <5 yrs. ER = 2.5% (−0.8, 6.0) Asthma HA's for children <5 yrs. ER = 2.6% (−4.0, 9.7) Pneumonia HA's for children <1 yrs. ER = 4.7% (0.7, 8.8)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America (cont'd)			
Rosas et al. (1998) SW Mexico City (1991) Population = NR PM_{10} mean. =77 $\mu g/m^3$ PM_{10} min/max= 25/183 $\mu g/m^3$	Log-regression analysis of relations between emergency hospital admissions for asthma for children <15 yrs (mean=2.5/day), adults (mean=3.0/day), and adults >59 yrs (mean=0.65/day) and lag 0-2 d pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	Few statistical associations were found between asthma admissions and air pollutants. Grass pollen was associated with child and adult admissions, and fungal spores with child admissions. Authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR
Australia			
Morgan et al. (1998) Sydney, AU (90 - 94) Population = NR $PM_{2.5}$ 24 h mean = 9.6 $\mu g/m^3$ $PM_{2.5}$ 10th-90th% = 3.6-18 $\mu g/m^3$ $PM_{2.5}$ max-1 h mean = 22.8 $\mu g/m^3$ $PM_{2.5}$ 10th-90th% = 7.5-44.4 $\mu g/m^3$	A Poisson analysis, controlled for overdispersion and autocorrelation via GEE, of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day)), COPD (mean 65+yrs =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM. The authors cited the error introduced by estimating $PM_{2.5}$ and the low PM levels as possible reasons for the weak PM-respiratory HA associations.	Asthma HA's Single Pollutant Model: For 24 hr $PM_{2.5}$ = 25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = −1.5% (CI: −7.8, 5.3) 15-64 yrs.(lag0) ER = 2.3% (CI: −4, 9) For 1h $PM_{2.5}$ =25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = + 0.5% (CI: −1.9, 3.0) 15-64 yrs.(lag0) ER = 1.5% (CI: −0.9, 4) Multiple Pollutant Model: For 24h $PM_{2.5}$ = 25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = −0.6% (CI: −7.4, 6.7) COPD (65+yrs.) Single Pollutant Model: For 24h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER =4.2% (CI: −1.5, 10.3) For 1h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER = 2% (CI: −0.3, 4.4) Multiple Pollutant Model: For 1h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER = 1.5% (CI: −0.9, 4)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Asia			
Tanaka et al. (1998) Stdy Pd.:1/92-12/93 Kushiro, Japan Pop. = 102 adult asthmatics PM_{10} mean = 24.0 $\mu g/m^3$ PM_{10} IQR = NR	Associations of HA's for asthma (in 44 non-atopic and 58 atopic patients) with weather or air pollutants (NO, NO_2, SO_2, PM_{10}, O_3, and acid fog) evaluated. Odds ratios (OR) and 95% CI's calculated between high and low days for each environmental variable. Poisson regression was performed for the same dichototomized variables.	Only the presence of acid fog had a significant OR >1.0 for both atopics and non-atopics. PM_{10} associated with a reduction in risk (OR<1.0) for both atopics and non-atopics. Poisson regression gave a non-significant effect by PM_{10} on asthma HA's. However, no long-wave or serial auto-correlation controls applied, so the opposing seasonalities of PM vs. HA's indicated in time series data plots are likely confounding these results.	For same-day (lag=0) PM_{10} Adult Asthma HA's OR for <30 vs. >30 $\mu g/m^3 PM_{10}$: Non-atopic OR = 0.77 (CI: 0.61, 0.98) Atopic OR = 0.87 (CI: 0.75, 1.02) Poisson Coefficient for PM_{10} > 30 $\mu g/m^3$ Non-atopic B = -0.01 (SE = 0.15) Atopic B = -0.002 (SE = 0.09)
Wong et al. (1999) Study Period.: 94 - 95 Hong Kong Population = NR PM_{10} mean = 50.1 $\mu g/m^3$ PM_{10} median = 45.0 $\mu g/m^3$ PM_{10} IQR = 30.7, 65.5 $\mu g/m^3$	Poisson regression analyses were applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated. Using the APHEA protocol, models accounted for time trend, season and other cyclical factors, T, RH, autocorrelation and overdispersion. PM_{10} measured by TEOM, which likely underestimates mass.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}. No significant respiratory HA interactions with PM_{10} effect were found for high NO_2, high O_3, or cold season.	PM_{10} = 50 $\mu g/m^3$ (Lags = 0-3 days) Respiratory HA's All age: ER = 8.3% (CI: 5.1, 11.5) 0-4yrs.: ER = 9.9% (CI: 5.4, 14.5) 5-64yrs.: ER = 8.8% (CI: 4.3, 13.4) 65+ yrs.: ER = 9.3% (CI: 5.1, 13.7) Asthma HA's (all ages) ER = 7.7% (1.0, 14.9) COPD HA's (all ages) ER = 10.0% (5.6, 14.3) Pneumonia and Influenza HA's (all ages) ER = 13.1% (7.2, 19.4)

Appendix 8B.3: PM-Respiratory Visits Studies

TABLE 8B-3. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Choudhury et al. (1997) Anchorage, Alaska (90 - 92) Population = 240,000 PM_{10} mean = 41.5 $\mu g/m^3$ PM_{10} (SD) = 40.87 PM_{10} maximum=565 $\mu g/m^3$	Using insurance claims data for state employees and dependents living in Anchorage, Alaska, number of daily medical visits determined for asthma (mean = 2.42/day), bronchitis, and upper respiratory infections. Used linear regression, including a time-trend variable, crude season indicator variables (i.e., spring, summer, fall, winter), and a variable for the month following a volcanic eruption in 1992.	Positive association observed between asthma visits and PM_{10}. Strongest association with concurrent-day PM_{10} levels. No co-pollutants considered. Temperature and RH did not predict visits, but did interact with the PM_{10} association. Morbidity relative risk higher with respect to PM_{10} pollution during warmer days.	Asthma Medical Visits (all ages): For mean = 50 $\mu g/m^3$ PM_{10} (single poll.) Lag = 0 days ER = 20.9% (CI: 11.8, 30.8)
Lipsett et al. (1997) Santa Clara County, CA Population = NR (Winters 88 - 92) PM_{10} mean = 61.2 $\mu g/m^3$ PM_{10} Min/Max = 9/165 $\mu g/m^3$	Asthma emergency department (ER) visits from 3 acute care hospitals (mean=7.6/day) related to CoH, NO_2, PM_{10}, and O_3 using Poisson model with long-wave, day of week, holiday, and weather controls (analysis stratified by minimum T). Every other day PM_{10} estimated from CoH. Residential wood combustion (RWC) reportedly a major source of winter PM. Gastro-enteritis (G-E) ER admissions also analyzed as a control disease.	Consistent relationships found between asthma ER visits and PM_{10}, with greatest effect at lower temperatures. Sensitivity analyses supported these findings. NO_2 also associated, but in simultaneous regressions only PM_{10} stayed associated. ER visits for gastroenteritis not significantly associated with air pollution. Results demonstrate an association between wintertime ambient PM_{10} and asthma exacerbations in an area where RWC is a principal PM source.	Asthma ED Visits (all ages) PM_{10} = 50 $\mu g/m^3$ (2 day lag): At 20° F, ER = 34.7% (CI: 16, 56.5) At 30° F, ER = 22% (CI: 11, 34.2) At 41° F, ER = 9.1% (CI: 2.7, 15.9)
Norris et al. (1999) Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 $\mu g/m^3$ PM_{10} IQR = 11.6 $\mu g/m^3$ σ_{sp} mean = 0.4 $m^{-1}/10^{-4}$ ($\approx$12.0 $\mu g/m^3$ $PM_{2.5}$) σ_{sp} IQR = 0.3 $m^{-1}/10^{-4}$ (= 9.5 $\mu g/m^3$ $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) were compared with those from lower hospital utilization areas(1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering (σ_{sp}), CO, SO_2, and NO_2 using a semiparametric Poisson regression model evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. There was no stronger association between ED visits for asthma and air pollution in the higher hospital utilization area than in the lower utilization area in terms of RR's. However, considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city.	Children's (<18 yrs.) Asthma ED Visits Single Pollutant Models: 24h PM_{10} =50 $\mu g/m^3$ Lag1 ER = 75.9% (25.1, 147.4) For 25 $\mu g/m^3$ $PM_{2.5}$ Lag1 ER = 44.5% (CI: 21.7, 71.4) Multiple Pollutant Models: 24h PM_{10} =50 $\mu g/m^3$ Lag1 ER = 75.9% (CI: 16.3, 166) For 25$\mu g/m^3$ $PM_{2.5}$ Lag1 ER = 51.2% (CI: 23.4, 85.2)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Norris et al. (2000) Spokane, WA (1/95 - 3/97) Population = 300,000 PM_{10} mean. = 27.9 μg/m^3 PM_{10} Min/Max =4.7/186.4 μg/m^3 PM_{10} IQR = 21.4 μg/m^3 Seattle, WA (9/95 - 12/96) Pop. Of Children <18 = 107,816 PM_{10} mean. = 21.5 μg/m^3 PM_{10} Min/Max = 8/69.3 μg/m^3 PM_{10} IQR = 11.7 μg/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yr. (mean=3.2/d) in Spokane and for children <18 yr. (mean=1.8/d) in Seattle. Poisson GAM model applied, controlling for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in both cities. Factor analysis indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with "stagnation" as the "co-pollutant" indicated importance of general air pollution over any single air pollutant index, but not of the importance of various pollutants relative to each other.	Asthma ED Visits Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 50 μg/m^3 Lag 3 ER = 2.4% (CI: −10.9, 17.6) Persons<18 years (Seattle) For PM_{10} IQR = 50 μg/m^3 Lag 3 ER = 56.2% (95 CI: 10.4 , 121.1)
Tolbert et al. (2000b) Atlanta, GA (92 - 94 Summers) Population = 80% of children in total population of 3 million PM_{10} mn. (SE) = 38.9 (15.5) μg/m^3 PM_{10} Range = 9, 105 μg/m^3	Pediatric (<17 yrs. of age) ED visits (mean = 467/day) related to air pollution (PM_{10}, O_3, NO_x, pollen and mold) using GEE and logistic regression and Bayesian models. Autocorrelation, day of week, long-term trend terms, and linear temperature controls included.	Both PM_{10} and O_3 positively associated with asthma ED visits using all three modeling approaches. In models with both O_3 and PM_{10}, both pollutants become non-significant because of high collinearity of the variables (r=0.75).	Pediatric (<17 yrs. of age) ED Visits PM_{10} = 50 μg/m^3 Lag 1 day ER = 13.2% (CI: 1.2, 26.7) With O_3 8.2 (−7.1, 26.1)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			

Tolbert et al. (2000a)
Atlanta
Period 1: 1/1/93-7/31/98
Mean, median, SD:
PM_{10} (μg/m^3): 30.1, 28.0, 12.4
 	
Period 2: 8/1/98-8/31/99
Mean, median, SD:
PM_{10} (μg/m^3): 29.1, 27.6, 12.0
$PM_{2.5}$ (μg/m^3): 19.4, 17.5, 9.35
CP (μg/m^3): 9.39, 8.95, 4.52 10-100 nm PM counts
(count/cm^3): 15,200, 10,900, 26,600
10-100 nm PM surface area
(um^2/cm^3): 62.5, 43.4, 116
$PM_{2.5}$ soluble metals (μg/m^3): 0.0327, 0.0226, 0.0306
$PM_{2.5}$ Sulfates (μg/m^3): 5.59, 4.67, 3.6
$PM_{2.5}$ Acidity (μg/m^3): 0.0181, 0.0112, 0.0219
$PM_{2.5}$ organic PM (μg/m^3): 6.30, 5.90, 3.16
$PM_{2.5}$ elemental carbon (μg/m^3): 2.25, 1.88, 1.74
	Preliminary analysis of daily emergency department (ED) visits for asthma (493), wheezing (786.09) COPD (491, 492, 4966) LRI 466.1, 480, 481, 482, 483, 484, 485, 486), all resp disease (460-466, 477, 480-486, 491, 492, 493, 496, 786.09) for persons $\geq$16 yr in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all DVD in period 1 were 6.5 and 28.4, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day-of-week and hospital entry/exit indicators also included. Pollutants treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, observed significant COPD association with 3-day average PM_{10}. COPD was also positively associated with NO_2, O_3, CO and SO_2. No statistically significant association observed between asthma and PM_{10} in period 1. However, asthma positively associated with ozone (p=0.03). In period 2, i.e., the first year of operation of the superstation, no statistically significant associations observed with PM_{10} or $PM_{2.5}$. These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Period 1:
			<u>Period 1:</u>
			PM_{10} (0-2 d):
			  asthma:
			    5.6% (−8.6, 22.1)
			  COPD:
			    19.9% (0.1, 43.7)
			
			<u>Period 2:</u> (all 0-2 day lag)
			PM_{10}: asthma
			    18.8% (−8.7, 54.4)
			  COPD
			    −3.5% (29.9 − 33.0)
			$PM_{2.5}$: asthma
			    2.3% (−14.8, 22.7)
			  COPD
			    12.4% (−7.9, 37.2)
			$PM_{10-2.5}$: asthma
			    21.1% (−18.2, 79.3)
			  COPD
			    −23.0% (50.7 − 20.1)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Yang et al (1997) Study Period: 92 - 94 Reno-Sparks, Nevada Population = 298,000 PM_{10} mean = 33.6 $\mu g/m^3$ PM_{10} range = 2.2, 157.3 $\mu g/m^3$	Association between asthma ER visits (mean = 1.75/d, SD=1.53/d) and PM_{10}, CO and O_3 assessed using linear WLS and ARIMA regression, including adjustments for day-of-week, season, and temperature (but not RH or T-RH interaction). Season adjusted only crudely, using month dummy variable.	Only O_3 showed significant associations with asthma ER visits. However, the crude season adjustment and linear model (rather than Poisson) may have adversely affected results. Also, Beta-gauge PM_{10} mass index used, rather than direct gravimetric mass measurements.	NR
Canada			
Delfino et al. (1997) Montreal, Canada Population= 3 million 6-9/92, 6-9/93 1993 Means (SD): PM_{10}= 21.7 $\mu g/m^3$ (10.2) $PM_{2.5}$= 12.2 $\mu g/m^3$ (7.1) $SO_4^=$= 34.8 $nmol/m^3$ (33.1) H^+= 4 $nmol/m^3$ (5.2)	Association of daily respiratory emergency department (ED) visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using linear regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons aged 2-64 yrs. For patients >64 yr, O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ positively associated with visits (p < 0.02), but PM effects smaller than for O_3.	Respiratory ED Visits Adults >64: (pollutant lags = 1 day) 50 $\mu g/m^3$ PM_{10} ER = 36.6% (10.0, 63.2) 25 $\mu g/m^3$ $PM_{2.5}$ ER = 23.9% (4.9, 42.8)
Delfino et al. (1998) Montreal, Canada 6-8/89,6-8/90 Mean PM_{10}= 18.6 $\mu g/m^3$ (SD=9.3, 90th% = 30.0 $\mu g/m^3$)	Examined the relationship of daily ED visits for respiratory illnesses by age (mean/day: <2yr.=8.9; 2-34yr.=20.1; 35-64yr.=22.6; >64yr.=20.3) with O_3 and estimated $PM_{2.5}$. Seasonal and day-of-week trends, auto-correlation, relative humidity and temperature were addressed in linear time series regressions.	There was an association between $PM_{2.5}$ and respiratory ED visits for older adults (>64), but this was confounded by both temperature and O_3. The fact that $PM_{2.5}$ was estimated, rather than measured, may have weakened its relationship with ED visits, relative to O_3.	Older Adults(>64 yr) Respiratory ED Visits Estimated $PM_{2.5}$ = 25 $\mu g/m^3$ Single Pollutant: (lag 1 $PM_{2.5}$) ER = 13.2 (−0.2, 26.6) With Ozone (lag 1 $PM_{2.5}$): Est. $PM_{2.5}$ (lag1) ER = 0.8% (CI: −14.4, 15.8)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Stieb et al. (1996) New Brunswick, Canada Population = 75,000 May-Sept. 84 - 92 SO_4^{2-} Mean = 5.5 μg/m³ Range: 1-23, 95th% =14 μg/m³ TSP Mean = 36.7 μg/m³ Range:5-108, 95th% =70 μg/m³	Asthma ED visits (mean=1.6/day) related to daily O_3 and other air pollutants (SO_2, NO_2, SO_4^{2-}, and TSP). PM measured only every 6th day. Weather variables included temperature, humidex, dewpoint, and RH. ED visit frequencies were filtered to remove day of week and long wave trends. Filtered values were regressed on pollution and weather variables for the same day and the 3 previous days.	Positive, statistically significant (p < 0.05) association observed between O_3 and asthma ED visits 2 days later; strength of the association greater in nonlinear models. Ozone effect not significantly influenced by addition of other pollutants. However, given limited number of sampling days for sulfate and TSP, it was concluded that "a particulate effect could not be ruled out".	Emergency Department Visits (all ages) Single Pollutant Model 100 μg/m³ TSP = 10.7% (-66.4, 87.8)
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} (μg/m³): 14.0, 9.0 $PM_{2.5}$ (μg/m³): 8.5, 5.9 H+ (nmol/m³): 25.7, 36.8 Sulfate (nmol/m³): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for asthma (mean 3.5/day), COPD (mean 1.3/day), resp infections (mean 6.2/day), and all respiratory conditions (mean 10.9/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations were observed between all respiratory ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations were observed with H+, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions.	$PM_{2.5}$, (lag 3) 15.1 (−0.2, 32.8) PM_{10}, (lag 3) 32.5 (10.2, 59.3)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe			
Atkinson et al. (1999a) London (92 - 94) Population = NR PM10 Mean = 28.5 μg/m³ 10th-90th IQR = 15.8-46.5 μg/m³ BS mean =12.7 μg/m³ 10th-90th IQR = 5.5-21.6 μg/m³	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits from 12 London hospitals considered, but associated population size not reported. Counts for ages 0-14, 15-64, and >64 also examined. Poisson regression used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	PM_{10} positively associated, but not BS, for all-age/all-respiratory category. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship. PM_{10} positively associated for all ages, children, and young adults for asthma ED visits. However, PM_{10}-asthma relationship couldn't be separated from SO_2 in multi-pollutant regressions. Older adult ED visits most strongly associated with CO. No O_3-ED visits relationships found (but no warm season analyses attempted).	PM_{10} (50 μg/m³) No co-pollutant: <u>All Respiratory ED visits</u> All age(lag 1d)ER = 4.9% (CI: 1.3, 8.6) <15yrs(lag 2d)ER = 6.4% (CI: 1, 12.2) 15-64yr(lag1d)ER = 8.6% (CI: 3.4, 14) <u>Asthma ED visits</u> All age (lag 1d) ER = 8.9% (CI: 3, 15.2) <15yrs (lag 2d) ER = 12.3% (CI: 3.4, 22) 15-64yr (lg 1d) ER = 13% (CI: 4.6, 22.1) PM_{10} (50 μg/m³) 2d lag & co-pollutant: Children's (<15 yrs.) Asthma ED Visits: PM alone: ER = 12.3% (CI: 3.4, 22) &NO₂: ER = 7.8% (CI: −1.2, 17.6) & O₃: ER = 10.5% (CI: 1.6, 20.1) & SO₂: ER = 8.1% (CI: −1.1, 18.2) & CO: ER = 12.1% (CI: 3.2, 21.7)
Hajat et al. (1999) London, England (92 - 94) Population = 282,000 PM₁₀ mean = 28.2 μg/m³ PM₁₀ 10t-90th%=16.3-46.4 μg/m³ BS mean = 10.1 μg/m³ BS 10t-90th%=4.5-15.9 μg/m³	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care general practitioner asthma and "other LRD" consultations. Asthma consultation means per day = 35.3 (all ages); 14.(0-14 yrs,); 17.7 (15-64 yrs.); 3.6 (>64 yrs.). LRD means = 155 (all ages); 39.7(0-14 yrs,); 73.8 (15-64 yrs.); 41.1 (>64 yrs.). Time-series analyses of daily numbers of consultations performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children. Authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In adults, the authors concluded that the only consistent association was with PM_{10}. Across all of the various age, cause, and season categories considered, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits:</u> 50 μg/m³ PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 5.4% (CI: −0.6, 11.7) 0-14 yrs.(lg 1): ER = 6.4% (−1.5, 14.6) 15-64 yrs.(lg 0): ER = 9.2% (CI: 2.8, 15.9) >64yrs.(lg 2): ER = 11.7% (−1.8, 26.9) -Year-round, 2 Pollutant, Children (0, 14): (PM_{10} lag = 1 day) PM_{10} ER's: W/NO₂: ER = 0.8% (CI: −8.7, 11.4) W/O₃: ER = 5.5% (−2.1, 13.8) W/SO₂: ER = 3.2% (CI: −6.4, 13.7) <u>Other Lower Resp. Dis. Doctor's Visits:</u> 50 μg/m³ PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 3.5% (CI: 0, 7.1) 0-14 yrs.(lg 1): ER = 4.2% (CI: −1.2, 9.9) 15-64 yrs.(lg 2): ER= 3.7% (CI: 0.0, 7.6) >64yrs.(lg 2): ER = 6.2% (CI: 0.5, 12.9)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hajat et al. (2001) London (1992-1994) 44,406-49,596 registered patients <1 to 14 years PM_{10} mean 28.5 (13.9)	Daily physician consultations (mean daily 4.8 for children; 15.3 for adults) for allergic rhinitis (ICD-9, 477), SO_2, O_3, NO_2, CO, PM_{10}, and pollen using generalized additive models with nonparametric smoother.	SO_2 and O_3 show strong associations with the number of consultations for allergic rhinitis. Estimates largest for a lag of 3 or 4 days prior to consultations, with cumulative measures stronger than single day lags. Stronger effects were found for children than adults. The two-pollutant analysis of the children's model showed that PM_{10} and NO_2 associations disappeared once either SO_2 or O_3 was incorporated into the model.	PM_{10} - Increment (10-90%) (15.8-46.5) Age <1-14 years lag 3: 10.4 (2.0 to 19.4) Cum 0-3: 17.4 (6.8 to 29.0) Ages 15-64 years lag 2: 7.1 (2.6 to 11.7) Cum 0-6: 20.2 (14.1 to 26.6)
Medina et al. (1997) Greater Paris 91 - 95 Population.= 6.5 MM Mean PM_{13} = 25 $\mu g/m^3$ PM_{13} min/max = 6/95 $\mu g/m^3$ Mean BS = 21 $\mu g/m^3$ BS min/max = 3/130 $\mu g/m^3$	Evaluated short-term relationships between PM_{13} and BS concentrations and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris. Poisson regression used, with non-parametric smoothing functions controlling for time trend, seasonal patterns, pollen counts, influenza epidemics, day-of-week, holidays, and weather.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results also indicate that air pollutant associations noted for hospital ED visits are also applicable to a wider population that visits their doctor.	Doctor's Asthma House Visits: 50 $\mu g/m^3$ PM_{13} Year-round, Single Pollutant: All ages (lg 2): ER = 12.7% (CI: 4.1, 21.9) 0-14 yrs.(lg 0-3): ER = 41.5% (CI: 20, 66.8) 15-64 yrs.(lg 2): ER = 6.3% (CI: −4.6, 18.5)
Damiá et al. (1999) Valencia, Spain (3/94-3/95) Population = NR BS mean = 101 $\mu g/m^3$ BS range = 34-213 $\mu g/m^3$	Associations of BS and SO_2 with weekly total ED admissions for asthma patients aged > 12 yrs (mean = 10/week) at one hospital over one year assessed, using linear stepwise regression. Season-specific analyses done for each of 4 seasons, but no other long-wave controls. Linear T, RH, BP, rain, and wind speed included as crude weather controls in ANOVA models.	Both BS and SO_2 correlated with ED admissions for asthma (SO_2: r=0.32; BS: r=0.35), but only BS significant in stepwise multiple regression. No linear relationship found with weather variables. Stratified ANOVA found strongest BS-ED association in the autumn and during above average temperatures. Uncontrolled autocorrelation (e.g., within-season) and weather effects likely remain in models.	Asthma ED Visits (all ages): BS = 40 $\mu g/m^3$ (single pollutant) BS as a lag 0 weekly average: ER = 41.5% (CI = 39.1, 43.9)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Pantazopoulou et al. (1995) Athens, GR (1988) Population = NR Winter (1/88-3/88,9/88-12/88) BS mean. =75 $\mu g/m^3$ BS 5th-95th %=26 - 161 $\mu g/m^3$ Summer (3/22/88-3/88,9/21/88) BS mean. =55 $\mu g/m^3$ BS 5th-95th %=19 - 90 $\mu g/m^3$	Examined effects of air pollution on daily emergency outpatient visits and admissions for cardiac and respiratory causes. Air pollutants included: BS, CO, and NO_2. Multiple linear regression models used, controlling for linear effects of temperature and RH, day of week, holidays, and dummy variables for month to crudely control for season, separately for winter and summer.	Daily number of emergency visits related positively with each air pollutant, but only reached nominal level of statistical significance for NO_2 in winter. However, the very limited time for each within-season analysis (6 mo.) undoubtably limited the power of this analysis to detect significant effects. Also, possible lagged pollution effects were apparently not investigated, which may have reduced effect estimates.	Single Pollutant Models For Winter (BS = 25 $\mu g/m^3$) <u>Outpatient Hospital Visits</u> ER = 1.1% (−0.7, 2.3) <u>Respiratory HA's</u> ER = 4.3% (0.2, 8.3) For Summer, BS = 25 $\mu g/m^3$ <u>Outpatient Hospital Visits</u> ER = 0.6% (−4.7, 6.0)) <u>Respiratory HA's</u> ER = 5.5% (−3.6, 14.7)
Garty et al. (1998) PM_{10} mean ≈ 45 $\mu g/m^3$ Tel Aviv, Israel (1993)	Seven day running mean of asthma ED visits by children (1-18 yrs.) to a pediatric hospital modeled in relation to PM_{10} in Tel Aviv, Israel.	No PM_{10} associations found with ED visits. The ER visits–pollutant correlation increased significantly when the September peak was excluded. Use of a week-long average and associated uncontrolled long-wave fluctuations (with resultant autocorrelation) likely prevented meaningful analyses of short –term PM associations with ED visits.	N/A

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin Amercia			
IIabaca et al. (1999) Santiago, Chile February 1995-August 1996 PM_{10}: warm: 80.3 $\mu g/m^3$ cold: 123.9 $\mu g/m^3$ $PM_{2.5}$: warm: 34.3 $\mu g/m^3$ cold: 71.3 $\mu g/m^3$	Number of daily respiratory emergency visits (REVs) related to PM by Poisson model smooths for longer- and short-term trends. SO_2, NO_2, O_3.	Stronger coefficients for models including $PM_{2.5}$ than for models including PM_{10} or $PM_{10-2.5}$. Copollutant effects were significantly associated with REVs. For respiratory patients, the median number of days between the onset of the first symptoms and REV was two to three days. For the majority of patients (70%) this corresponded to the lag observed in this study indicating that the timing of the pollutant effect is consistent with the temporal pattern of REV in this population.	REV, lag 2 Cold $PM_{2.5}$, lag 2 OR: 1.027 (1.01 to 1.04) for a 45 $\mu g/m^3$ increment PM_{10}, lag 2 OR: 1.02 (1.01 to 1.04) for a 76 $\mu g/m^3$ increment $PM_{2.5}$, lag 2 OR: 1.01 (1.00* to 1.03) for a 32 $\mu g/m^3$ increment Pneumonia, lag 2 PM_{10}: 1.05 (1.00* to 1.10) 64 $\mu g/m^3$ increment $PM_{2.5}$: 1.04 (1.00* to 1.09) 45 $\mu g/m^3$ increment $PM_{10-2.5}$: 10.5 (1.00* to 1.10) 32 $\mu g/m^3$ increment *decimals <1.00

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin Amercia (cont'd)			
Lin et al. (1999) Sao Paulo, BR (91-93) Population=NR PM_{10} mean =65 μg/m³ PM_{10} SD=27 μg/m³ PM_{10} range=15-193 μg/m³	Respiratory ED visits by children (0-12 yrs.) To a major pediatric hospital (mean=56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower respiratory (mean = 8/day) and upper respiratory (mean = 9/day) all evaluated. Analyses considered effects of season, day of week, and extreme weather (using T, RH dummy variables).	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants all simultaneously added to the model. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models. More than 20% increase in ED visits found on the most polluted days, "indicating that air pollution is a substantial pediatric health concern".	50 μg/m³ PM_{10} (0-5-day lag mean) Respiratory ED Visits (<13 yrs.) Single pollutant model: PM_{10} ER=21.7% (CI: 18.2, 25.2) All pollutant models: PM_{10} ER=28.8% (CI: 21.4, 36.7) Lower Respiratory ED Visits (<13 yrs.) Single pollutant model: PM_{10} ER=22.8% (CI: 12.7, 33.9) All pollutant models: PM_{10} ER=46.9% (CI: 27.9, 68.8)
Ostro et al. (1999b) Santiago, CI (7/92—12/93) <2 yrs. Population ≈ 20,800 3-14 yrs. Population ≈ 128,000 PM_{10} mean. =108.6 μg/m³ PM_{10} Min/Max=18.5/380 μg/m³ PM_{10} IQR = 70.3 – 135.5 μg/m³	Analysis of daily visits to primary health care clinics for upper (URS) or lower respiratory symptoms (LRS) for children 2-14 yr (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2 yr. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 μg/m³) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	Lower Resp. Symptoms Clinic Visits PM_{10} = 50 μg/m³ Single Pollutant Models: -Children<2 years Lag 3 ER = 2.5% (CI: 0.2, 4.8) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.8, 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (CI: 0, 4.4) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.9, 6.5)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Australia			
Smith et al. (1996) Stdy Pd.: 12/92-1/93,12/93-1/94 West Sydney, AU Population = 907,000 -Period 1 (12/92-1/93) B_{scatt} median = 0.25 10^{-4}/m B_{scatt} IQR = 0.18-0.39 10^{-4}/m B_{scatt} 95th% = 0.86 10^{-4}/m -Period 2 (12/93-1/94) B_{scatt} median = 0.19 10^{-4}/m B_{scatt} IQR = 0.1-0.38 10^{-4}/m B_{scatt} 95^{th}5% = 3.26 10^{-4}/m PM_{10} median = 18 $\mu g/m^3$ PM_{10} IQR = 11.5-28.8 $\mu g/m^3$ PM_{10} 95th% = 92.5 $\mu g/m^3$	Study evaluated whether asthma visits to emergency departments (ED) in western Sydney (mean≈10/day) increased as result of bushfire-generated PM (B_{scatt} from nephelometry) in Jan., 1994 (period 2). Air pollution data included nephelometry (B_{scatt}), PM_{10}, SO_2, and NO_2. Data analyzed using two methods: (1) calculation of the difference in proportion of all asthma ED visits between the time periods, and; (2) Poisson regression analyses. Control variables included T, RH, BP, WS, and rainfall.	No difference found in the proportion of all asthma ED visits during a week of bushfire-generated air pollution, compared with the same week 12 months before, after adjusting for baseline changes over the 12-month period. The max. B_{scatt} reading was not a significant predictor of the daily asthma ED visits in Poisson regressions. However, no long-wave controls applied, other than indep. vars., and the power to detect differences was weak (90% for a 50% difference). Thus, the lack of a difference may be due to low statistical strength or to lower toxicity of particles from burning vegetation at ambient conditions vs. fossil fuel combustion.	ED Asthma Visits (all ages) Percent change between bushfire and non bushfire weeks: PM_{10} = 50 $\mu g/m^3$ ER = 2.1% (CI: -0.2, 4.5)
Asia			
Ye et al. (2001) Tokyo, Japan Summer months July-August, 1980-1995 PM_{10} 46.0 mean	Hospital emergency transports for respiratory disease for >65 years of age were related to pollutant levels NO_2, O_3, PM_{10}, SO_2, and CO.	For chronic bronchitis PM_{10} with a lag time of 2 days was the most statistically significant model covariate.	Asthma (ICD-9-493) Coefficienct estimate (SE) 0.003 (0.001)
Chew et al. (1999) Singapore (90 - 94) Population = NR TSP mean = 51.2 $\mu g/m^3$ TSP SD = 20.3 $\mu g/m^3$ TSP range = 13-184 $\mu g/m^3$	Child (3-13 yrs.) ED visits (mean = 12.8/day) and HA's (mean = 12.2/day) for asthma related to levels of SO_2, NO_2, TSP, and O_3 using linear regression with weather, day-of-week controls. Auto-correlation effects controlled by including prior day response variable as a regression variable. Separate analyses done for adolescents (13-21 yrs.) (mean ED=12.2, mean HA=3.0/day).	Positive associations found between TSP, SO_2, and NO_2, and daily HA and ED visits for asthma in children, but only with ED visits among adolescents. Lack of power (low counts) for adolescents' HA's appears to have been a factor in the lack of associations. When ED visits stratified by year, SO_2 and TSP remained associated in every year, but not NO_2. Analyses for control diseases (appendicitis and urinary tract infections) found no associations.	TSP(100 $\mu g/m^3$) No co-pollutant: Child (3-13 yrs.)Asthma ED visits Lag 1d ER = 541% (CI: 198.4, 1276.8)

Appendix 8B.4: Pulmonary Function Studies

TABLE 8B-4. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	The O_3-ΔPEFR relationship was seen as the strongest.	—
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} measurements were made using a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 $\mu g/m^3$.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	In general, PM_{10} was associated with changes in both peak flow and respiratory symptoms. Ozone, SO_2, and sulfate levels were low because of low vehicle admissions.	Lag 0, PM_{10} average PEF- -0.27 (-0.54, -0.01) per 10 $\mu g/m^3$ increment
Europe			
Gielen et al. (1997) Amsterdam, NL Mean PM_{10} level: 30.5 $\mu g/m^3$ (16, 60.3). Mean maximum 8 hr O_3: 67 $\mu g/m^3$.	Study evaluated 61 children aged 7 to 13 years living in Amsterdam, The Netherlands. 77 percent of the children were taking asthma medication and the others were being hospitalized for respiratory problems. Peak flow measurements were taken twice daily. Associations of air pollution were evaluated using time series analyses. The analyses adjusted for pollen counts, time trend, and day of week.	The strongest relationships were found with ozone, although some significant relationships found with PM_{10}.	Lag 0, PM_{10}: Evening PEF = -0.08 (-2.49, 2.42) Lag 1, PM_{10}: Morning PEF = 1.38 (-0.58, 3.35) Lag 2, PM_{10}: Morning PEF = 0.34 (-1.78, 2.46) Evening PEF = -1.46 (-3.23, 0.32)
Hiltermann et al. (1998) Leiden, NL July-Oct, 1995 O_3, NO_2, SO_2, BS, and PM_{10} ranged from 16.4 to 97.9 $\mu g/m^3$)	270 adult asthmatic patients from an out-patient clinic in Leiden, The Netherlands were studied from July 3 to October 6, 1995. Peak flow measured twice daily. An autoregressive model was fitted to the data. Covariates included temp. and day of week. Individual responses not modeled.	No relationship between ozone or PM_{10} and PFT was found	Lag 0, PM_{10}: Average PEF = -0.80 (-3.84, 2.04) 7 day ave., PM_{10}: Average PEF = -1.10 (-5.22, 3.02)

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Peters et al. (1996) Erfurt and Weimar, Germany SO_2, TSP, PM_{10}, sulfate fraction, and PSA. Mean PM_{10} level was 112 $\mu g/m^3$. PM was measured by a Marple-Harvard impactor.	Panel of 155 asthmatic children in the cities of Erfurt and Weimar, E. Germany studied. Each panelist's mean PEF over the entire period subtracted from the PEF value to obtain a deviation. Mean deviation for all panelists on given day was analyzed using an autoregressive moving average. Regression analyses done separately for adults and children in each city and winter; then combined results calculated.	Five day average SO_2 was associated with decreased PEF. Changes in PEF were not associated with PM levels.	—

Peters et al. (1997b)
Erfurt, Germany
PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}.
Particles measured using size cuts of 0.01 to 0.1, 0.1 to 0.5, and 0.5 to 2.5 μm.
Mean PM_{10} level: 55 $\mu g/m^3$ (max 71). Mean SO_2: 100 $\mu g/m^3$ (max 383).
PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.
	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season of 1991-1992. Morning and evening peak flow readings recorded. An auto-regressive model was used to analyze deviations in individual peak flow values, including terms for time trend, temp., humidity, and wind speed and direction.	Strongest effects on peak flow found with ultrafine particles. The two smallest fractions, 0.01 to 0.1 and 0.1 to 0.5 were associated with a decrease of PEF.	Lag 0, PM_{10}:
			  Evening PEF = −0.38 (−1.83, 1.08)
			Lag 1, PM_{10}:
			  Morning PEF = −1.30 (−2.36, 0.24)
			5 Day Mean, PM_{10}:
			  Morning PEF = −1.51 (−3.20, 0.19)
			  Evening PEF = −2.31 (−4.54, −0.08)
			Lag 0, $PM_{2.5}$:
			  Evening PEF = −0.75 (−1.66, 0.17)
			Lag 1, $PM_{2.5}$:
			  Morning PEF = −0.71 (−1.30, 0.12)
			5 Day Mean, $PM_{2.5}$:
			  Morning PEF = −1.19 (−1.81, 0.57)
			  Evening PEF = −1.79 (−2.64, −0.95)

Peters et al. (1997c)
Sckolov, Czech Republic
Winter 1991-1992
PM_{10}, SO_2, TSP, sulfate, and particle strong acid.
Median PM_{10} level: 47 $\mu g/m^3$ (29, 73).
Median SO_2: 46 $\mu g/m^3$ (22, 88).
PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.
	89 children with asthma in Sokolov, Czech Republic studied. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. The analysis used linear regression for PFT. First order autocorrelations were observed and corrected for using polynomial distributed lag (PDL) structures.	Five day mean SO_2, sulfates, and particle strong acidity were also associated with decreases in PM PFT as well as PM_{10}.	Lag 0, PM_{10}:
			  Morning PEF = −0.71 (−2.14, 0.70)
			  Evening PEF = −0.92 (−1.96, 0.12)
			5 Day mean PM_{10}:
			  Evening PEF = −1.72 (−3.64, 0.19)
			  Morning PEF = −0.94 (−2.76, 0.91)

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Timonen and Pekkanen (1997) Kupio, Finland PM_{10}, BS, NO_2, and SO_2. The intequartile range on PM_{10} was 8 to 23.	Studied 74 asthmatic children (7 to 12 yr) in Kuoio, Finland. Daily mean PEF deviation calculated for each child. Values were analyzed, then using linear first-order autoregressive model. PM was measured using single stage Harvard Impactors.	Lagged concentrations of NO_2 related to declines in morning PEF as well as PM_{10} and BS.	
Penttinen et al. (2001) studied adult asthmatics for 6 months in Helsinki, Findland. PM was measured using a single-stage Harvard impactor. Particle number concentrations were measured using an Electric Aerosol Spectrometer. $NO_2 PM_{10}$ ranged from 3.8 to 73.7 $\mu g/m^3$. $PM_{2.5}$ ranged from 2.4 to 38.3 $\mu g/m^3$.	57 asthmatics were followed with daily PEF measurements and symptom and medications diaries from November 1996 to April 1997. PEF deviations from averages were used as dependent variables. Independent variables included PM_1, $PM_{2.5}$, PM_{10}, particle counts, CO, NO, and	The strongest relationships were found between PEF deviations and PM particles below 0.1 μm. No associations were found between particulate pollution and respiratory symptoms.	AM PEF = -.115 (-.448, .218) $PM_{2.5}$, lag one day AM PEF = -.001 (-.334, .332) $PM_{2.5}$ lag two days
Pekkanen et al. (1997) Kuopio, Finland PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 18 $\mu g/m^3$ (10, 23). Mean NO_2 level: 28 $\mu g/m^3$.	Studied 39 asthmatic children aged 7-12 years living in Kuopio, Finland. Changes in peak flow measurements were analyzed using a linear first-order autoregressive model. PM was measured using single stage Harvard impactors.	Changes in peak flow found to be related to all measures of PM, after adjusting for minimum temperature. PN0.032-0.10 (1/cm³) and PN1.0-3.2 (1/cm³) were most strongly associated with morning PEF deviations.	Lag 0, PM_{10}: Evening PEF = -0.35 (-1.14, 0.96) Lag 1, PM_{10}: Morning PEF = -2.70 (-6.65, 1.23) Lag 2, PM_{10}: Morning PEF = -4.35 (-8.02, -0.67) Evening PEF = -1.10 (-4.70, 2.50) Small sized particles had relationships similar to those of PM_{10} for morning and evening PEF.
Segala et al. (1998) Paris, France Nov. 1992 - May 1993. BS, SO_2, NO_2, PM_{13} (instead of PM_{10}), measured. Mean PM_{13} level: 34.2 $\mu g/m^3$ (range 8.8, 95). Mean SO_2 level: 21.7 $\mu g/m^3$ (range 4.4, 83.8). Mean NO_2 level: 56.9 $\mu g/m^3$ (range 23.8, 121.9). PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 years living in Paris, France from Nov. 15, 1992 to May 9, 1993. Peak flow measured three times a day. Covariates in the model included temperature and humidity. An autoregressive model was fitted to the data using GEE methods.	Effects found related to PM_{10} were less than those found related to the other pollutants. The strongest effects were found with SO_2.	Lag 4, PM_{13}: Morning PEF = -0.62 (-1.52, 0.28)
Gauvin et al. (1999) Grenoble, France Summer 1996, Winter 1997 Mean (SD) $\mu g/m^3$ PM_{10} Summer 23 (6.7) PM_{10} Winter 38 (17.3) Sunday 15.55 (5.12) Weekday 24.03 (7.2)	Two panels: mild adult asthmatics, ages 20-60 years, (summer-18 asthmatics, 20 control subjects; winter-19 asthmatics, 21 control subjects) were examined daily for FEV_1 and PEF. Bronchial reactivity was compared Sunday vs. weekday. Temperature and RH controlled.	Respiratory function decreased among asthmatic subjects a few days (lag 2/4 days) after daily PM_{10} levels had increased. Bronchial reactivity was not significantly different between the weekdays and weekends. No copollutant analysis conducted.	For a 10 $\mu g/m^3$ increase in PM_{10} Summer FEV_1 -1.25% (-0.58 to -1.92) PEF -0.87% (-0.1 to -1.63)

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM$_{10}$ (25 μg/m^3 PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Agócs et al. (1997) Budapest, Hungary SO2 and TSP were measured. TSP was measured by beta reactive absorption methods.	Panel of 60 asthmatic children studied for two months in Budapest, Hungary. Mixed model used relating TSP to morning and evening PEFR measurements, adjusting for SO$_2$, time trend, day of week, temp., humidity		No significant TSP-PEFR relationships found.
Australia			
Rutherford et al. (1999) Brisbane, Australia PM$_{10}$, TSP, and particle diameter. PM$_{10}$ ranged form 11.4 to 158.6 μg/m^3. Particle sizing was done by a Coulter Multisizer.	Study examined effects of 11 dust events on peak flow and symptoms of people with asthma in Brisbane, Australia. PEF data for each individual averaged for a period of 7 days prior to the identified event. This mean was compared to the average for several days of PEF after the event, and the difference was tested using a paired t-test.	The paired t-tests were stat. significant for some days, but not others. No general conclusions could be drawn.	—
Latin America			
Romieu et al. (1996) Mexico City, Mexico During study period, maximum daily 1-h O$_3$ ranged from 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave, PM$_{10}$ levels ranged from 29 to 363 μg/m^3 (mean 166.8 μg/m^3, SD 72.8 μg/m^3). For 53 percent of study days, PM$_{10}$ levels exceeded 150 μg/m^3. PM$_{10}$ was measured by a Harvard impactor.	Study of 71 children with mild asthma aged 5-7 years living in the northern area of Mexico City. Morning and evening peak flow measurements recorded by parents. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. Model included terms for minimum temperature.	Ozone strongly related to changes in morning PEF as well as PM$_{10}$.	Lag 0, PM$_{10}$: Evening PEF = −4.80 (−8.00, −1.70) Lag 2, PM$_{10}$: Evening PEF = −3.65 (−7.20, 0.03) Lag 0, PM$_{2.5}$: Evening PEF = −4.27 (−7.12, −0.85) Lag 2, PM$_{2.5}$: Evening PEF = −2.55 (−7.84, 2.74) Lag 1, PM$_{10}$ Morning PEF = −4.70 (−7.65, −1.7) Lag 2, PM$_{10}$ Morning PEF = −4.90 (−8.4, −1.5)
Romieu et al. (1997) Mexico City, Mexico During study period, maximum daily 1-h ozone ranged from 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM$_{10}$ daily average ranged from 12 to 126 μg/m^3. PM$_{10}$ was measured by a Harvard impactor.	Study of 65 children with mild asthma aged 5-13 yr in southwest Mexico City. Morning and evening peak flow measurements made by parents. Peak flow measurements standardized for each person and model was fitted using GEE methods. Model included terms for minimum temperature.	Strongest relationships were found between ozone (lag 0 or 1) and both morning and evening PFT.	Lag 0, PM$_{10}$: Evening PEF = −1.32 (−6.82, 4.17) Lag 2, PM$_{10}$: Evening PEF = −0.04 (−4.29, 4.21) Morning PEF = 2.47 (−1.75, 6.75) Lag 0, PM$_{10}$: Morning PEF = 0.65 (−3.97, 5.32)

**Appendix 8B.5: Short-Term PM Exposure Effects
On Symptoms in Asthmatic Individuals**

TABLE 8B-5. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Delfino et al. (1996) San Diego, CA Sept-Oct 1993 Ozone and $PM_{2.5}$ measured. PM was measured by a Harvard impactor. $PM_{2.5}$ ranged from 6 to 66 $\mu g/m^3$ with a mean of 25.	Study of 12 asthmatic children with history of bronchodilator use. A random effects model was fitted for ordinal symptoms scores and bronchodilator use in relation to 24-hr $PM_{2.5}$.	Pollen not associated with asthma symptom scores. 12-hr personal O_3 but not ambient O_3 related to symptoms.	No significant relationships with PM_{10}.
Delfino et al. (1997) San Diego County, CA PM_{10} and ozone PM was measured using a tapered-element oscillating microbalance. PM_{10} ranged from 6 to 51 $\mu g/m^3$ with a mean of 26.	A panel of 9 adults and 13 children were followed during late spring 1994 in semi-rural area of San Diego County at the inversion zone elevation of around 1,200 feet. A random effects model was fitted to ordinal symptom scores, bronchodilator use, and PEF in relation to 24-hour PM_{10}. Temp., relative humidity, fugal spores, day of week and O_3 evaluated	Although PM_{10} never exceeded 51 $\mu g/m^3$, bronchodilator use was significantly associated with PM_{10}(0.76 [0.027, 0.27]) puffs per 50 $\mu g/m^3$. Fungal spores were associated with all respiratory outcomes.	—
Delfino et al. (1998) So. California community Aug. - Oct. 1995 Highest 24-hour PM_{10} mean: 54 $\mu g/m^3$. PM_{10} and ozone PM was measured using a tapered-element oscillating microbalance. PM_{10} ranged from 6 to 51 $\mu g/m^3$ with a mean of 26.	Relationship of asthma symptoms to O_3 and PM_{10} examined in a So. California community with high O_3 and low PM. Panel of 25 asthmatics ages 9 - 17 followed daily, Aug. - Oct., 1995. Longitudinal regression analyses utilized GEE model controlling for autocorrelation, day of week, outdoor fungi and weather.	Asthma symptoms scores significantly associated with both outdoor O_3 and PM_{10} in single pollutant and co-regressions. 1-hr and 8-hr maxi PM_{10} had larger effects than 24-hr mean.	24-h - 1.47 (0.90-2.39) 8-h - 2.17 (1.33-3.58) 1-h - 1.78 (1.25-2.53)
Yu et al. (2000) study of a panel of 133 children aged 5-12 years in Seattle, WA. PM was measured by gravimetric and nephelometry methods. $PM_{1.0}$ ranged from 2 to 62 $\mu g/m^3$ with a mean of 10.4. PM_{10} 9 to 86 $\mu g/m^3$ mean 24.7.	Daily diary records were collected from November 1993 through August 1995 during screening for the CAMP study. A repeated measures logistic regression analysis was used applied using GEE methods	One day lag CO and PM_{10} levels and the same day PM_{10} and S)2 levels had the strongest effects on asthma symptoms after controlling for subject specific variables and time-dependent confounders.	OR symptom = 1.18 (1.05, 1.33) (PM_{10} same day) OR symptom = 1.17 (1.04, 1.33) (PM_{10} one day lag)
Ostro et al. (2001) studied exacerbation of asthma in African-American children in Los Angeles. PM was measured by a beta-attenuated Andersen monitor. PM_{10} ranged from 21 to 119 $\mu g/m^3$ with a mean of 51.8.	138 children aged 8 to 13 years who had physician diagnosed asthma were included. A daily diary was used to record symptoms and medication use. GEE methods were used to estimate the effects of air pollution on symptoms controlling for meteorological and temporal variables.	Symptoms were generally related to PM_{10} and NO_2, but not to ozone. Reported associations were for pollutant variables lagged 3 days. Results for other lag times were not reported.	24-h OR wheeze = 1.02 (0.99, 106))PM_{10} lag 3 days) OR cough = 1.06 (1.02, 1.09) (PM_{10} lag 3 days) OR shortness of breath = 1.08 (1.02, 1.13) (PM_{10} lag 3 days) 1-h OR cough = 1.05 (1.02, 1.18) lag 3 days

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OFASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m³ PM$_{10}$ (25 μg/m³ PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Thurston et al. (1997) Summers 1991-1993. O$_3$, H+, sulfate, pollen, daily max temp. measured.	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	Ozone related to respiratory symptoms No relationship between symptoms and other pollutants.	—
Canada			
Vedal et al. (1998) PM$_{10}$ measured by Sierra-Anderson dichotomous sampler PM$_{10}$ range: −1 to 159 μg/m³ Port Alberrni British, Columbia	206 children aged 6 to 13 years, 75 with physician's diagnosis of asthma. Respiratory symptom data from diaries, GEE model. Temp., humidity.	PM$_{10}$ associated with respiratory symptoms.	Lag 0 Cough OR = 1.08 (1.00, 1.16) per 10 μg/m³ PM$_{10}$ increments
Europe			
Gielen et al. (1997) Amsterdam, NL PM$_{10}$ and ozone. PM$_{10}$ was measured using a Sierra-Anderson dichotomous sampler. PM$_{10}$ ranged from 15 to 60 μg/m³.	Study of 61 children aged 7 to 13 years living in Amsterdam, NL. 77 percent were taking asthma medication and the others were being hospitalized for respiratory problems. Respiratory symptoms recorded by parents in diary. Associations of air pollution evaluated using time series analyses, adjusted for pollen counts, time trend, and day of week.	Strongest relationships found with O$_3$, although some significant relationships found with PM$_{10}$.	Lag 0, Symptoms: Cough OR = 2.19 (0.77, 6.20) Bronch. Dial. OR = 0.94 (0.59, 1.50) Lag 2, Symptoms: Cough OR = 2.19 (0.47, 10.24) Bronch. Dial. OR = 2.90 (1.80, 4.66)
Hiltermann et al. (1998) Leiden, NL July-Oct 1995. Ozone, PM$_{10}$, NO$_2$, SO$_2$, BS PM$_{10}$ ranged from 16 to 98 μg/m³ with a mean of 40.	Study of 270 adult asthmatic patients from an out-patient clinic in Leiden, NL from July 3, to October 6, 1995. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data. Covariates included temperature and day of week.	PM$_{10}$, O$_3$, and NO$_2$ were associated with changes in respiratory symptoms.	Lag 0, Symptoms: Cough OR = 0.93 (0.83, 1.04) Short. breath OR = 1.17 (1.03, 1.34) 7 day average, Symptoms: Cough OR = 0.94 (0.82, 1.08) Short. breath OR = 1.01 (0.86, 1.20)
Hiltermann et al. (1997) The Netherlands Ozone and PM$_{10}$ PM$_{10}$ averaged 40 μg/m³,	Sixty outpatient asthmatics examined for nasal inflammatory parameters in The Netherlands from July 3 to October 6, 1995. Associations of log transformed inflammatory parameters to 24-h PM$_{10}$ analyzed, using a linear regression model. Mugwort-pollen and O$_3$ were evaluated.	Inflammatory parameters in nasal lavage of patients with intermittent to severe persistent asthma were associated with ambient O$_3$ and allergen exposure, but not with PM$_{10}$ exposure.	—

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Peters et al. (1997b) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 55 $\mu g/m^3$ (max 71). Mean SO_2: 100 $\mu g/m^3$ (max 383). PM was measured using a Harvard impactor.	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season 1991-1992. Diary used to record presence of cough. Symptom information analyzed using multiple logistic regression analysis.	Weak associations found with 5 day mean sulfates and respiratory symptoms.	Lag 0, PM_{10}: Cough OR = 1.32 (1.16, 1.50) Feeling ill OR = 1.20 (1.01, 1.44) 5 Day Mean, PM_{10}: Cough OR = 1.30 (1.09, 1.55) Feeling ill OR = 1.47 (1.16, 1.86) Lag 0, $PM_{2.5}$: Cough OR = 1.19 (1.07, 1.33) Feeling ill OR = 1.24 (1.09, 1.41) 5 Day Mean, $PM_{2.5}$: Cough OR = 1.02 (0.91, 1.15) Feeling ill OR = 1.21 (1.06, 1.38)
Peters et al. (1997c) Sokolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10}: 47 $\mu g/m^3$ (29, 73). Median SO_2: 46 $\mu g/m^3$ (22, 88). PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Study of 89 children with asthma in Sokolov, Czech Republic. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. Logistic regression for binary outcomes used. First order autocorrelations were observed and corrected for using polynomial distributed lag structures.	Significant relationships found between TSP and sulfate with both phlegm and runny nose.	Lag 0, Symptoms: Cough OR = 1.01 (0.97, 1.07) Phlegm OR = 1.13 (1.04, 1.23) 5 Day Mean, Symptoms: Cough OR = 1.10 (1.04, 1.17) Phlegm OR = 1.17 (1.09, 1.27)
Peters et al. (1997c) Sokolov, Czech Republic PM_{10} one central site. SO_4 reported. Mean PM_{10}: 55 $\mu g/m^3$, max 177 $\mu g/m^3$. SO_4 - fine: mean 8.8 $\mu g/m^3$, max 23.8 $\mu g/m^3$. PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Role of medication use evaluated in panel study of 82 children, mean ages 9.8 yr., with mild asthma in Sokolov, Czech Republic Nov. 1991 - Feb 1992. Linear and logistic regression evaluated PM_{10}, SO_2, temp, RH relationships to respiratory symptoms.	Medicated children, as opposed to those not using asthma medication, increased their beta-agonist use in direct association with increases in 5-day mean of SO_4 particles <2.5 μm, but medication did not prevent decrease in PEF and increase in prevalence of cough attributable to PM air pollution.	Cough 1.16 (1.00, 1.34) 6.5 $\mu g/m^3$ increase 5-day mean SO_4 5-d Mean SO_4/increase of 6.5 $\mu g/m^3$ Beta-Agonist Use 1.46 (1.08, 1.98) Theophylline Use 0.99 (0.77, 1.26) No PM_{10} analysis
Neukirch et al. (1998) Paris, France SO_2, NO_2, PM_{13} and BS. PM was measured by radiometry. PM_{13} ranged from 9 to 95 $\mu g/m^3$ with a mean of 34.	Panel of 40 nonsmoking adult asthmatics in Paris studied. GEE models used to associate health outcomes with air pollutants. Models allowed for time-dependent covariates, adjusting for time trends, day of week, temp. and humidity.	Significant relationships found for incidence of respiratory symptoms and three or more day lags of SO_2, and NO_2. Only selected results were given.	Significant relationships found between incidence of respiratory symptoms and three or more day lags of PM_{13}.

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Segala et al. (1998) Paris, France SO_2, NO_2, PM_{13} (instead of PM_{10}), and BS. PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 yr in Paris. Patients followed Nov. 15, 1992 to May 9, 1993. Respiratory symptoms recorded daily in diary. An autoregressive model fitted to data using GEE methods. Covariates included temp. and humidity.	Effects found related to PM_{13} were less than those found related to the other pollutants.	Lag 2, Symptoms: Short. Breath OR = 1.22 (0.83, 1.81) Resp. Infect. OR = 1.66 (0.84, 3.30)
Güntzel et al. (1996) Switzerland SO_2, NO_2, TSP	An asthma reporting system was used in connection with pollutant monitoring in Switzerland from fall of 1988 to fall 1990. A Box-Jenkins ARIMA time series model was used to relate asthma to TSP, O_3, SO_2, and NO_2 after adjusting for temperature.	No significant relationships found.	—
Taggart et al. (1996) Northern England SO_2, NO_2 and BS.	Panel of 38 adult asthmatics studied July 17 to Sept. 22, 1993 in northern England. Used generalized linear model to relate pollutants to bronchial hyper-responsiveness, adjusting for temperature.	Small effects seen in relation to NO_2 and BS.	—
Latin America			
Romieu et al. (1997) Mexico City, Mexico During study period, max daily 1-h O_3 range: 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average range: 12 to 126 $\mu g/m^3$. PM was measured by a Harvard impactor.	Study of 65 children with mild asthma aged 5-13 yr living in southwest Mexico City. Respiratory symptoms recorded by the parents in daily diary. An autoregressive logistic regression model used to analyze presence of respiratory symptoms.	Strongest relationships found between O_3 and respiratory symptoms.	Lag 0, Symptoms: Cough OR = 1.05 (0.92, 1.18) Phlegm OR = 1.05 (0.83, 1.36) Diff. Breath OR = 1.13 (0.95, 1.33) Lag 2, Symptoms: Cough OR = 1.00 (0.92, 1.10) Phlegm OR = 1.00 (0.86, 1.16) Diff. Breath OR = 1.2 (1.1, 1.36)
Romieu et al. (1996) During study period, max daily range: 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave. PM_{10} levels range: 29 to 363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). PM_{10} levels exceeded 150 $\mu g/m^3$ for 53% of study days. 24-h ave. $PM_{2.5}$ levels range 23-177 $\mu g/m^3$ (mean 85.7 $\mu g/m^3$) PM was measured by a Harvard impactor.	Study of 71 children with mild asthma aged 5-7 yr living in northern Mexico City. Respiratory symptoms recorded by parents in daily diary. An autoregressive logistic regression model was used to analyze the presence of respiratory symptoms.	Cough and LRI were associated with increased O_3 and PM_{10} levels.	PM_{10} (lag 0) increase of 50 $\mu g/m^3$ related to: LRI = 1.21 (1.10, 1.42) Cough = 1.27 (1.16, 1.42) Phlegm = 1.21 (1.00, 1.48) $PM_{2.5}$ (lag 0) increase of 25 $\mu g/m^3$ related to: LRI = 1.18 (1.05, 1.36) Cough = 1.21 (1.05, 1.39) Phlegm = 1.21 (1.03, 1.42)

**Appendix 8B.6: Short-Term PM Exposure Effects
On Pulmonary Function in Nonasthmatics**

TABLE 8B-6. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Hoek et al. (1998) (summary paper)	Results summarized from several other studies reported in the literature. These included: asymptomatic children in the Utah Valley (Pope et al., 1991), children in Bennekom, NL (Roemer et al., 1993), children in Uniontown, PA (Neas et al., 1995), and children in State College, PA (Neas et al., 1996). Analyses done using a first-order autoregressive model with adjustments for time trend and ambient temp.	Other pollutants not considered.	Significant decreases in peak flow found to be related to PM_{10} increases.
Lee and Shy (1999) North Carolina Mean 24 h PM_{10} conc. over two years: 25.1 $\mu g/m^3$.	Study of the respiratory health status of residents whose households lived in six communities near an incinerator in southwestern North Carolina. Daily PEFR measured in the afternoon was regressed against 24 hour PM_{10} level lagged by one day. Results were adjusted for gender, age, height, and hypersensitivity.	PM_{10} was not related to variations in respiratory health as measured by PEFR.	—
Korrick et al. (1998) Mt. Washington, NH O_3 levels measured at 2 sites near top of the mountain. $PM_{2.5}$ measured near base of the mountain. PM was measured by a Harvard impactor.	Study of the effects of air pollution on adult hikers on Mt. Washington, NH. Linear and non-linear regressions used to evaluate effects of pollution on lung function.	$PM_{2.5}$ had no effect on the O_3 regression coefficient.	—
Naeher et al. (1999) Virginia PM_{10}, $PM_{2.5}$, sulfate fraction, H+, and ozone	Daily change in PEF studied in 473 non-smoking women in Virginia during summers 1995-1996. Separate regression models run, using normalized morning and evening PEF for each individual.	Ozone was only pollutant related to evening PEF.	Morning PEF decrements were associated with PM_{10}, $PM_{2.5}$, and H+. Estimated effect from $PM_{2.5}$ and PM_{10} was similar. No PM effects found for evening PEF.
Neas et al. (1996) State College, PA $PM_{2.1}$: mean 23.5; max 85.8 $\mu g/m^3$.	Study of 108 children in State College, PA, during summer of 1991 for daily variations in symptoms and PEFRs in relation to $PM_{2.1}$ An autoregressive linear regression model was used. The regression was weighted by reciprocal number of children of each reporting period. Fungus spore conc., temp., O_3 and SO_2 were examined.	Spore concentration associated with deficient in morning PERF.	$PM_{2.1}$ (25 $\mu g/m^3$) related to RR of: PM PFER (lag 0) = −0.05 (−1.73, 0.63) PM PEFR (lag 1) = −0.64 (−1.73, 0.44)

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Neas et al. (1999) Philadelphia, PA Median PM_{10} level: 31.6 in SW camps, 27.8 in NE camps (IQR ranges of about 18). Median $PM_{2.5}$ level: 22.2 in the SW camps, 20.7 in NE camps (IQR ranges about 16.2 and 12.9, respectively). Particle-strong acidity, fine sulfate particle, and O_3 also measured.	Panel study of 156 normal children attending YMCA and YWCA summer camps in greater Philadelphia area in 1993. Children followed for at most 54 days. Morning and evening deviations of each child's PEF were analyzed using a mixed-effects model adjusting for autocorrelation. Covariates included time trend and temp. Lags not used in the analysis.	Analyses that included sulfate fraction and O_3 separately also found relationship to decreased flow. No analyses reported for multiple pollutant models.	Lag 0, PM_{10}: Morning PEF = -8.16 ($-$14.81, $-$1.55) Evening PEF = -1.44 ($-$7.33, 4.44) 5 day ave, PM_{10} Morning PEF = 2.64 ($-$6.56, 11.83) Evening PEF = 1.47 ($-$7.31, 10.22) Lag 0, $PM_{2.5}$ Morning PEF = $-$3.28 ($-$6.64, 0.07) Evening PEF = $-$0.91 ($-$4.04, 2.21) 5 day ave., $PM_{2.5}$ Morning PEF = 3.18 ($-$2.64, 9.02) Evening PEF = 0.95 ($-$4.69, 6.57)
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$) measured. Summary levels not given.	Analyses for 1844 school children in grades 2-5 from six urban areas in eastern U.S. and from separate studies from Uniontown and State College, PA. Lower resp. symptoms, cough and PEF used as endpoints. The authors replicated models used in the original analyses. CM and were used individually and jointly in the analyses. Sulfate fractions also used in the analyses. Details of models not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and, not surprisingly, gave similar answers.	Uniontown Lag 0, $PM_{2.5}$: Evening PEF = $-$1.52 ($-$2.80, $-$0.24) State College Lag 0, $PM_{2.5}$: Evening PEF = $-$0.93 ($-$1.88, 0.01) Results presented for CM showed no effect. Results for PM_{10} were not given.
Linn et al. (1996) So. California NO_2 ozone, and PM_5 measured. PM_5 was measured using a Marple low volume sampler PM_5 ranged from 1-145 $\mu g/m^3$ with a mean of 24.	Study of 269 school children in Southern California twice daily for one week in fall, winter and spring for two years. A repeated measures analysis of covariance was used to fit an autoregressive model, adjusting for year, season, day of week, and temperature.	Morning FVC was significantly decreased as a function of PM_5 and NO_2	—
Europe			
Boezen et al. (1999) Netherlands PM_{10}, BS, SO_2, and NO_2 measured, but methods were not given. PM_{10} ranged from 4.8 to 145 $\mu g/m^3$ with site means ranging from 26 to 54 $\mu g/m^3$.	Data collected from children during three winters (1992-1995) in rural and urban areas of The Netherlands. Study attempted to investigate whether children with bronchial hyperresponsiveness and high serum Ige levels were more susceptible to air pollution. Prevalence of a 10 percent PEF decrease was related to pollutants for children with bronchial hyperresponsiveness and high serum Ige levels.	No consistent pattern of effects observed with any of the pollutants for 0, 1, and 2 day lags.	—

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m³ PM_{10} (25 μg/m³ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Frischer et al. (1999) Austria PM_{10} measured gravimettrically for 14-d periods. Annual mean PM_{10} levels range: 13.6 - 22.9 μg/m³. O_3 range: 39.1 ppb - 18.5 pbs between sites.	At nine sites in Austria during 1994, 1995, and 1996, a longitudinal study designed to evaluate O_3 was conducted. During 1994 - 1996, children were measured for FVC, FEV_1 and MEF_{50} six times, twice a year in spring and fall. 1060 children provided valid function tests. Mean age 7.8 ± 0.7 yr. GEE models used. PM_{10}, SO_2, NO_2, and temp. evaluated.	Small but consistent lung function decrements in cohort of school children associated with ambient O_3 exposure.	PM_{10} showed little variation in exposure between study site. For PM_{10}, positive effect seen for winter exposure but was completely confounded by temperature. PM_{10} Summertime $\beta = 0.003$ SE 0.012 p=0.77
Grievink et al. (1999) Netherlands PM_{10} and BS. PM_{10} ranged from 12 to 123 μg/m³ with a mean of 44.	A panel of adults with chronic respiratory symptoms studied over two winters in The Netherlands starting in 1993/1994. Logistic regression analysis was used to model the prevalence of large PEF decrements. Individual linear regression analysis of PEF on PM was calculated and adjusted for time trends, influenza incidence, and meteorological variables.	Subjects with low levels of serum β-carotene more often had large PEF decrements when PM_{10} levels were higher, compared with subjects with high serum β-carotene. Results suggested serum β-carotene may attenuate the PM effects on decreased PEF.	—
Künzli et al. (2000)	Ackermann-Liebrich et al. (1997) data reanalyzed. Authors showed that a small change in FVC (-3.14 percent) can result in a 60% increase in number of subjects with FVC less than 80 percent of predicted.	The results were for two hypothetical communities, A and B.	—
Roemer et al. (2000) PM_{10} means for 17 panels ranged 11.2 to 98.8 μg/m³. SO_2, NO_2, and elemental content of PM also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Separate results reported by endpoints included symptoms as reported in a dairy and PEF. Individual panels were analyzed using multiple linear regression analysis on deviations from mean PEF adjusting for auto-correlation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	PM_{10} analyses not focus of this paper.
Scarlett et al. (1996) PM_{10}, O_3, and NO_2 measured.	In study of 154 school children, pulmonary function was measured daily for 31 days. Separate autoregressive models for each child were pooled, adjusting for pollen, machine, operator, time of day, and time trend.	PM_{10} was related to changes in FEV and FVC	—

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured.	Panel study of 795 children aged 7 to 11 years, with and without chronic respiratory symptoms living in urban and nonurban areas in the Netherlands. Peak flow measured for three winters starting in 1992/1993. Peak flow dichotomized at 10 and 20% decrements below the individual median. Number of subjects was used as a weight. Minimum temperature day of week, and time trend variables were used as covariates. Lags of 0, 1 and 2 days were used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No multiple pollutant models analyses reported.	Lag 0, PM_{10}, Urban areas Evening PEF OR = 1.15 (1.02, 1.29) Lag 2, PM_{10}, Urban areas Evening PEF OR = 1.07 (0.96, 1.19) 5 day ave, PM_{10}, Urban areas Evening PEF = 1.13 (0.96, 1.32)
van der Zee et al. (2000) Netherlands PM_{10} averages ranged 24 to 53 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured. PM_{10} was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of 489 adults aged 50-70 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Resp. symptoms and peak flow measured for three winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Peak flow dichotomized at 10 and 20% decrements below the individual median. The number of subjects used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	BS tended to have the most consistent relationship across endpoints. Sulfate fraction also related to increased respiratory effects. No analyses reported for multiple pollutant models. Relationship found between PM_{10} and the presence of 20% decrements in symptomatic subjects from urban areas.	Lag 0, PM_{10}, Urban areas Morning large decrements OR = 1.44 (1.02, 2.03) Lag 2, PM_{10}, Urban areas Morning large decrements OR = 1.14 (0.83, 1.58) 5 day ave, PM_{10}, Urban areas Morning large decrements OR = 1.16 (0.64, 2.10) Results should be viewed with caution because of problems in analysis.
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25th, 75th percentiles = 12, 43). Median $PM_{2.5}$ level: 15 (25th, 75th percentiles = 9, 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in the spring of 1995 in Kuopio, Finland. Morning and evening deviations of each child's PEF analyzed, using a general linear model estimated by PROC MIXED. Covariates included a time trend, day of week, temp., and humidity. Lags of 0 through 3 days were used, as well as a 4-day moving average. Various fine particles were examined.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly. Effects varied by lag. Separating effects by size was difficult.	Lag 0, PM_{10}: Morning PEF = 1.21 (−0.43, 2.85) Evening PEF = 0.72 (−0.63, 1.26) 4 day ave, PM_{10} Morning PEF = −1.26 (−5.86, 3.33) Evening PEF = 2.33 (−2.62, 7.28) Lag 0, $PM_{2.5}$ Morning PEF = 1.11 (−0.64, 2.86) Evening PEF = 0.70 (−0.81, 2.20) 4 day ave., $PM_{2.5}$ Morning PEF = −1.93 (−7.00, 3.15) Evening PEF = 1.52 (−3.91, 6.94)

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM$_{10}$ (25 μg/m^3 PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Ward et al. (2000) West Midlands, UK Daily measurements of PM$_{10}$, PM$_{2.5}$, SO$_2$, CO, O$_3$, and oxides of nitrogen. Details on PM monitoring were inomplete.	Panel study of 9 yr old children in West Midlands, UK for two 8-week periods representing winter and summer conditions. Individual PEF values converted to z-values. Mean of the z-values analyzed in a linear regression model, including terms for time trend, day of week, meteorological variables, and pollen count. Lags up to four days also used.	Results on effects of pollution on lung function to be published elsewhere.	—
Osunsanya et al. (2001) studied 44 patients aged > 50 with COPD in Aberdeen, UK. PM was measured using tapered element oscillating microbalance. Particle sizes were measured a TSI model 3934 scanning particle sizer. PM$_{10}$ ranged from 6 to 34 μg/m^3 with a median of 13.	Symptom scores, bronchodilator use, and PEF were recorded daily for three months. GEE methods were used to analyze the dichotomous outcome measures. PEF was converted to a dichotomous measure by defining a 10 percent decrement as the outcome of interest.	No associations were found between actual PEF and $_{PM10}$ or ultrafine particles. A change of $_{PM10}$ from 10 to 20 μg/m^3 was associated with a 14 percent decrease in the rate of high scores of shortness of breath. A similar change in PM$_{10}$ was associated with a rate of high scores of cough.	The endpoint was measured in terms of scores rather than L/min.
Cuijpers et al. (1994) Maastricht, NL SO$_2$, NO$_2$, BS, ozone, and H+ measured. PM measurements were made with a modified Sierra Anderson sampler. PM$_{10}$ ranged from 23 to 54 μg/m^3.	Summer episodes in Maastricht, The Netherlands studied. Paired t tests used for pulmonary function tests.	Small decreases in lung function found related to pollutants.	Quantitative results not given.
Latin America			
Gold et al. (1999) Mexico City, Mexico Mean 24 h O$_3$ levels: 52 ppb. Mean PM$_{2.5}$: 30 μg/m^3. Mean PM$_{10}$: 49 μg/m^3.	Peak flow studied in a panel of 40 school-aged children living in southwest Mexico City. Daily deviations from morning and afternoon PEFs calculated for each subject. Changes in PEF regressed on individual pollutants allowing for autocorrelation and including terms for daily temp., season, and time trend.	O$_3$ significantly contributed to observed decreases in lung function, but there was an independent PM effect.	Both PM$_{2.5}$ and PM$_{10}$ significantly related to decreases in morning and afternoon peak flow. Effects of the two pollutants similar in magnitude when compared on percent change basis.

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured. Details on monitoring methods and pollutant ranges were not given.	Study of 40 subjects aged over 55 years with COPD living in Christchurch, New Zealand conducted during winter of 1994. Subjects recorded their peak flow measurements. A log-linear regression model with adjustment for first order auto-correlation was used to analyze peak flow data and a Poisson regression model was used to analyze symptom data.	Few significant associations found between the health endpoints and the pollutants.	Lag 0, PM_{10}: PEF = -0.86 (-2.33, 0.61)
Jalaludin et al. (2000) studied PEF in 148 children 6 primary schools in Sydney, Australia. PM was measured by tapered element oscillating microbalance. Mean PM_{10} was 22.8 +- 13.9 $\mu g/m^3$.	148 children in grades 3-5 were followed for 11 months, recording PEF twice daily. The normalized change in PEF was analyzed using GEE methods. PEF was related to SO_3, PM_{10}, NO_2, as well as meteorological variables.	Daily mean deviations in PEF were related to ozone, but no relationships were found with PM_{10} or NO_2. Multiple pollutant models gave similar results to those given by the single pollutant models.	Change from AM to PM PEF = 0.045 (-.205, 2.95) lag one day
Asia			
Chen et al. (1999) Taiwan Beta-gauge PM_{10} ranged 44.5 to 189.0 $\mu g/m^3$ for peak concentrations.	In 3 Taiwan communities in 1995, PM_{10} by B-gauge measured at selected primary schools in each community. Spirometry tests (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, PEF) obtained in period May 1995 to Jan. 1996 using ATS protocol in study pop. aged 8 to 13 yr. 895 children were analyzed. Study was designed to investigate short-term effect of ambient air pollution in cross-sectional survey. Multivariate linear model analysis used in both one pollutant and multipollutant models, with 1-, 2-, and 7-day lags. SO_2, CO, O_3, NO_2 and PM_{10} examined, as were meteorol. variables.	In the one-pollutant model, daytime peak O_3 conc. with a 1-day lag significantly affected both FVC and FEV_1. NO_2, SO_2, CO affected FVC. PM_{10} showed nonsignificant decrement. No significant result demonstrated in the model for the exposure with 7 days lag. In the multi-pollutant model, only peak O_3 conc. with 1-day lag showed sig. effect on FVC and $FEV_{1.0}$.	One pollutant model daytime average PM_{10} – 2 day lag FVC -0.37 se 0.39
Tan et al. (2000) Southeast Asian smoke-haze event 9/29 – 10/27 1997 PM_{10} mean daily was 125.4 $\pm$ 44.9 $\mu g/m^3$ ultra range of 47 to 216 $\mu g/m^3$ in Singapore	Examined the association between acute air pollution caused by biomass burning and peripheral UBC counts in human serial measurement made during the event were compared with a period after the haze cleared (Nov. 21 – Dec. 5, 1997)	Indices of atmospheric pollution were significantly associated in the elevated band neutrophil counts expressed as a percentage of total polymonphonuclear leukocytes (PMN). No statistically significant difference in FEU_1 and FUC were observed during and after haze exposure.	

**Appendix 8B.7: Short-Term PM Exposure Effects
On Symptoms in Nonasthmatics**

TABLE 8B-7. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM$_{10}$ (25 μg/m^3 PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Schwartz and Neas (2000) Eastern U.S. PM$_{2.5}$ and CM (PM$_{10\text{-}2.5}$ by substation).. Summary levels not given	Reported on analysis of 1844 school children in grades 2–5 from six urban areas in the eastern U.S., and from separate studies from Uniontown and State College, PA. Lower respiratory symptoms, and cough used as endpoints. The authors replicated the models used in the original analyses. CM and PM$_{2.5}$ were used individually and jointly in the analyses. Sulfates fractions were also used in the analyses. Details of the models were not given.	Sulfate fraction was highly correlated with PM$_{2.5}$ (0.94), and not surprisingly gave similar answers.	PM$_{2.5}$ was found to be significantly related to lower respiratory symptoms even after adjusting for CM, whereas the reverse was not true. However, for cough, CM was found to be significantly related to lower respiratory symptoms even after adjusting for PM$_{2.5}$, whereas the reverse was not true.
Zhang et al. (2000) Vinton, Virginia 24- h PM$_{10}$, PM$_{2.5}$, sulfate and strong acid measured in 1995.	In southwestern Virginia, 673 mothers were followed June 10 to Aug. 31, 1995 for the daily reports of present or absence of runny or stuffy nose. PM indicator, O$_3$, NO$_2$ temp., and random sociodemographic characteristics considered.	Of all pollutants considered, only the level of coarse particles as calculated (PM$_{10}$ - PM$_{2.5}$) independently related to incidence of new episode of runny noses.	—
Canada			
Long et al. (1998) Winnepeg, CN PM$_{10}$, TSP, and VOC measured. Methods for PM monitoring not given. Ranges of values also not given.	Study of 428 participants with mild airway obstruction conducted during a Winnepeg pollution episode. Gender specific odds ratios of symptoms were calculated for differing PM$_{10}$ levels using the Breslow-Day test.	Cough, wheezing, chest tightness, and shortness of breath were all increased during the episode	—
Europe			
Boezen et al. (1998) Amsterdam, NL PM$_{10}$, SO$_2$, and NO$_2$ measured. PM$_{10}$ ranged from 7.9 to 242.2 μg/m^3 with a median of 43.	Study of 75 symptomatic and asymp. adults near Amsterdam for three months during winter 1993-1994. An autoregressive logistic model was used to relate PM$_{10}$ to respiratory symptoms, cough, and phlegm, adjusting for daily min. temp., time trend, day of week.	No relationship found with pulmonary function. Some significant relationships with respiratory disease found in subpopulations	—

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS
IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Howel et al. (2001) study of children's respiratory health in 10 non-urban communities of northern England. PM levels were measured using a single continuous real-time monitor. PM_{10} levels ranged from 5 to 54 $\mu g/m^3$.	The study included 5 pairs of non-urban communities near and not so near 5 coal mining sites. 1405 children aged 1-11 years were included. 275 of the children reported having asthma. Diaries of respiratory symptoms were collected over a 6 week period. PM_{10}, measured by a single continuous real-time monitor, ranged from 5 to 54 $\mu g/m^3$.	The associations found between daily PM_{10} levels and respiratory symptoms were frequently small and positive and sometimes varied by community.	OR wheeze = 1.16 (1.05, 1.28 (PM_{10}) OR cough = 1.09 (1.02, 1.16) (PM_{10}) OR reliever use = 1.00 (0.94, 1.06) (PM_{10})
Roemer et al. (1998) Mean PM_{10} levels measured at local sites ranged 11.2 to 98.8 $\mu g/m^3$ over the 28 sites.	Pollution Effects on Asthmatic Children in Europe (PEACE) study was a multi-center study of PM_{10}, BS, SO_2, and NO_2 on respiratory health of children with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Children with chronic respiratory symptoms were selected into the panels. The symptom with one of the larger selection percentages was dry cough (range over sample of study communities 29 to 92% [22/75; 84/91] with most values over 50%). The group as a whole characterized as those with chronic respiratory disease, especially cough.	These studies modeled group rates and are an example of the panel data problem.	—
Roemer et al. (2000) PM_{10} means for the 17 panels ranged 11.2 to 98.8 $\mu g/m^3$. SO_2, NO_2, and PM elemental content also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Endpoints included symptoms as reported in a dairy and PEF. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	The analysis of PM_{10} was not a focus of this paper.

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM$_{10}$ (25 μg/m^3 PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (1999) Netherlands PM$_{10}$ averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO$_2$, and NO$_2$ also measured.	A panel study of 795 children aged 7 to 11 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Respiratory symptoms measured for 3 winters starting 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. The number of subjects was used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM$_{10}$, BS and sulfate fraction and the health endpoints. No analyses reported with multiple pollutant models.	Lag 0, PM$_{10}$, Urban areas Cough OR = 1.04 (0.95, 1.14) Lag 2, PM$_{10}$, Urban areas Cough OR = 0.94 (0.89, 1.06) 5 day ave, PM$_{10}$, Urban areas Cough OR = 0.95 (0.80, 1.13)
van der Zee et al. (2000) Netherlands Daily measurements of PM$_{10}$, BS, fine sulfate, nitrate, ammonium and strong acidity. PM$_{10}$ was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of adults aged 50 to 70 yr during 3 consecutive winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. Analysis treated as a time series, adjusting for first order autocorrelation. Number of subjects used as a weight. Min. temp., day of week, time trend variables used as covariates. Lags 0, 1 and 2 days used, as well as 5 day moving average.	BS was associated with upper respiratory symptoms.	Lag 0, Symptoms, Urban areas LRS OR = 0.98 (0.89, 1.08) URS OR = 1.04 (0.96, 1.14) Lag 2, Symptoms, Urban areas LRS OR = 1.01 (0.93, 1.10) URS OR = 1.04 (0.96, 1.13) 5 day ave, Symptoms, Urban areas LRS OR = 0.95 (0.82, 1.11) URS OR = 1.17 (1.00, 1.37)
Tiittanen et al. (1999) Kupio, Finland Median PM$_{10}$ level: 28 (25th, 75th percentiles = 12, 43). Median PM$_{2.5}$: 15 (25th and 75th percentiles of 9 and 23). Black carbon, CO, SO$_2$, NO$_2$, and O$_3$ also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in spring 1995 in Kuopio, Finland. Cough, phlegm, URS, LRS and medication use analyzed, using a random effects logistic regression model (SAS macro GLIMMIX). Covariates included a time trend, day of week, temp., and humidity. Lags of 0 to 3 days used, as well as 4-day moving average.	Ozone strengthened the observed associations. Introducing either NO$_2$ or SO$_2$ in the model did not change the results markedly.	Lag 0, PM$_{10}$: Cough OR = 1.00 (0.87, 1.16) 4 day ave, PM$_{10}$ Cough OR = 1.58 (0.87, 2.83) Lag 0, PM$_{2.5}$ Cough OR = 1.04 (0.88, 1.23) 4 day ave., PM$_{2.5}$ Cough OR = 2.01 (1.04, 3.89)
Keles et al. (1999) Istanbul, Turkey Nov. 1996 to Jan. 1997. TSP levels ranged from annual mean of 22 μg/m^3 in unpolluted area to 148.8 μg/m^3 in polluted area.	Symptoms of rhinitis and atopic status were evaluated in 386 students grades 9 and 10 using statistical package for the social sciences, Fisher tests, and multiple regression model as Spearman's coefficient of correlation.	No difference found for atopic status in children living in area with different air pollution levels.	—

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM$_{10}$ (25 μg/m^3 PM$_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
New Zealand			
Harré et al. (1997) Christchurch, NZ SO$_2$, NO$_2$, PM$_{10}$, and CO measured. Details on monitoring methods and pollutant ranges were not given.	Study of 40 subjects aged 55 years with COPD living in Christchurch, New Zealand during winter 1994. Subjects recorded completed diaries twice daily. Poisson regression model used to analyze symptom data.	NO$_2$ was associated with increased bronchodilator use.	PM$_{10}$ was associated with increased nighttime chest symptoms.
Asia			
Awasthi et al. (1996) India Suspended particulate matter, SO$_2$, nitrates, coal, wood, PM and kerosene measured. SPM was measured using a high-volume sampler.	A cohort of 664 preschool children studied for two weeks each in northern India. Ordinary least squares was used to relate a respiratory symptom complex pollutants.	A significant regression coefficient between PM and symptoms was found	—

**Appendix 8B.8: Long-Term PM Exposure Effects On
Respiratory Health Indicators, Symptoms, and Lung Function**

TABLE 8B-8. LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States			
Abbey et al. (1998) California Communities 20 year exposure to respirable particulates, suspended sulfates, ozone, and PM_{10}. PM_{10} ranged from 1 to 145 $\mu g/m^3$ with a mean value of 32.8.	Sex specific multiple linear regressions were used to relate lung function measures to various pollutants in long-running cohort study of Seven Day Adventists (ASHMOG Study).	Sulfates were associated with decreases in FEV.	Frequency of days where $PM_{10} >$ 100 $\mu g/m^3$ associated with FEV decrement in males whose parents had asthma, bronchitis, emphysema, or hay fever. No effects seen in other subgroups.
Berglund et al.. (1999) California communities	Cohort study of Seventh Day Adventists. Multivariate logistic regression analysis of risk factors (e.g., PM) for chronic airway disease in elderly non-smokers, using pulmonary function test and respiratory symptom data.	Significant risk factors identified: childhood respiratory illness, reported ETS exposure, age, sex and parental history.	For $PM_{10} > 100 \mu g/m^3$, 42 d/yr: RR = −1.09 CT (0.92, 1.30) for obstructive disease determined by pulmonary function tests.
Peters et al. (1999a,b) 12 demographically similar communities in So. California. O_3, PM acids, and NO_2 evaluated. PM was measured using a tapered element oscillating microbalance instrument.	Stepwise logistic regression was used to relate prevalence rates for symptoms to community-specific ambient pollutants after adjustment for race, sex, asthma, body mass, hay fever, and membership in an insurance plan.	Wheeze prevalence was associated with both acid and NO_2.	No significant relationships were found between PM_{10} and symptoms.
Avol et al. (2001) Subjects living in Southern California in 1993 that moved to other western locations in 1998. Pollutants O_3, NO_2, PM_{10} differences 15 to 66 $\mu g/m^3$.	Studied 110 children who were 10 yrs of age at enrollment and 15 at follow-up who had moved from communities filled out health questions and underwent spirometry. Linear regression used to determine whether annual average change in lung function correlated with average changes in PM.	As a group, subjects who moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with a higher PM_{10} showed decreased growth in lung function.	PM_{10} 24 hr average PERF ml/s per 10 $\mu g/m^3$ mean = −34.9 95% CI −59.8, −10.1

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
Gauderman et al. (2000) 12 So. California communities 1993 to 1997 Pollutants: O_3, NO_2, PM_{10}, and $PM_{2.5}$. PM_{10} levels ranged from 16.1 to 67.6 $\mu g/m^3$ across the communities.	Studies of lung function growth of 3035 children in 12 communities within 200-mile radius of Los Angeles during 1993 to 1997. Cohorts of fourth, seventh, and tenth-graders studied. By grade cohort, a sequence of linear regression models were used to determine over the 4yr of follow-up, if average lung function growth rate of children was associated with average pollutant levels. Adjustment were made for height, weight, body mass index, height by age interaction, report of asthma activity or smoking. Two-pollutant models also used.	Lung growth rate for children in most polluted community, as compared to least polluted, was estimated to result in cumulative reduction of 3.4% in FEV_1 and 5.0% in MMEF over 4-yr study period. Estimated deficits mostly larger for children spending more time outdoors. Due to the high correlation in concentrations across communities, not able to separate effects of each pollutant. No sig. associations seen with O_3.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates were: −0.85% for PM_{10} (p = 0.026); −0.64% for $PM_{2.5}$ (p = 0.052); −0.90% for $PM_{10-2.5}$ (p = 0.030); −0.77% for NO_2 (p = 0.019); and −0.73% for inorganic acid vapor (p = 0.042).
McConnell et al. (1999) 12 Southern California communities 1994 air monitoring data. PM_{10} (mean 34.8; range 13.0 - 70.7 $\mu g/m^3$). $PM_{2.5}$ (yearly mean 2 week averaged mean 15.3 $\mu g/m^3$; range 6.7 - 31.5 $\mu g/m^3$).	Cross-sectional study of 3,676 school children whose parents completed questionnaires in 1993 that characterized the children's history of respiratory illness. Three groups examined: (1) history of asthma; (2) wheezing but no asthma; and (3) no history of asthma or wheezing. Logistic regression model used to analyze PM, O_3, NO_2, acid vapor effects. This study also described in Peters et al. (1999b,c).	Positive association between air pollution and bronchitis and phlegm observed only among children with asthma. As PM_{10} increased across communities, a corresponding increase in risk of bronchitis per interquartile range occurred. Strongest association with phlegm was for NO_2. Because of high correlation of PM air pollution, NO_2, and acid, not possible to distinguish clearly which most likely responsible for effects.	PM_{10} Asthma Bronchitis 1.4 CI (1.1 − 1.8) Phlegm 2.1 (1.4 − 3.3) Cough 1.1 (0.8 − 1.7) No Asthma / No Wheeze Bronchitis 0.7 (0.4 − 1.0) Phlegm 0.8 (0.6 − 1.3) Cough 0.9 (0.7 − 1.2)

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
McConnell et al. (2002) 12 Southern California communities 1994-1997 4-year mean conc. PM_{10} $\mu g/m^3$ High community: 43.3 (12.0) Low community: 21.6 (3.8)	In 3,535 children assessed, the association of playing team sports with subsequent development of asthma during 4 yrs of follow-up. Comparing high pollutant communities to low pollutant communities. Relative risks of asthma adjusted for ethnic origin were evaluated for every pollutant with a multivariate proportional hazards model. See also Peters et al. (1999b,c).	Across all communities there was a 1.8-fold increased risk (95% CI 1.2-2.8) for asthma in children who had played three or more team sports in the previous year. In high ozone (10:00 h to 18:00 h mean concentration) communities, there was a 3.3-fold increase risk of asthma in children playing three or more sports, an increase not seen in low ozone communities.	The effect of team sports was similar in communities with high and low PM with a small increase in asthma among children playing team sports.
Dockery et al. (1996) 24 communities in the U. S. and Canada. PM_{10}, $PM_{2.5}$, sulfate fraction, H^+, ozone, SO_2, and other measures of acid were monitored. PM was measured using a Harvard impactor. PM_{10} ranged form 15.4 to 32.7 with a mean of 23.8. $PM_{2.5}$ ranged form 5.8 to 20.7 $\mu g/m^3$ with a mean of 14.5.	Respiratory health effects among 13,369 white children aged 8 to 12 yrs analyzed in relation to PM indices. Two-stage logistic regression model used to adjust for gender, history of allergies, parental asthma, parental education, smoking in home.	Although bronchitis endpoint was significantly related to fine PM sulfates, no endpoints were related to PM_{10} levels.	—
Raizenne et al. (1996) 24 communities in the U.S. and Canada Pollutants measured for at least one year prior to lung function tests: PM_{10}, $PM_{2.1}$, particle strong acidity, O_3, NO_2, and SO_2. PM was measured with a Harvard impactor. For pollutant ranges, see Dockery et al. (1996).	Cross-sectional study of lung function. City specific adjusted means for FEV and FVC calculated by regressing the natural logarithm of the measure on sex, ln height, and ln age. These adjusted means were then regressed on the annual pollutant means for each city.	PM measures (e.g., particle strong acidity) associated with FEV and FVC decrement.	—

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe			
Ackermann-Liebrich et al. (1997) Eight Swiss regions Pollutants: SO_2, NO_2, TSP, O_3, and PM_{10}. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 53 $\mu g/m^3$ with a mean of 37.	Long-term effects of air pollution studied in cross-sectional population-based sample of adults aged 18 to 60 yrs. Random sample of 2,500 adults in each region drawn from registries of local inhabitants. Natural logarithms of FVC and FEV_1 regressed against natural logarithms of height, weight, age, gender, atopic status, and pollutant variables.	Significant and consistent effects on FVC and FEV were found for PM_{10}, NO_2 and SO_2.	Estimated regression coefficient for PM_{10} versus FVC = -0.035 (95% CI -0.041, -0.028). Corresponding value for FEV_1 -0.016 (95% CI -0.023 to -0.01). Thus, 10 $\mu g/m^3$ PM_{10} increase estimated to lead to estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.
Braun-Fahrländer et al. (1997) 10 Swiss communities Pollutants: PM_{10}, NO_2, SO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 $\mu g/m^3$.	Impacts of long-term air pollution exposure on respiratory symptoms and illnesses were evaluated in cross-sectional study of Swiss school children, (aged 6 to 15 years). Symptoms analyzed using a logistic regression model including covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others.	Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The colinearity of the pollutants including NO_2, SO_2, and O_3, prevented any causal separation.	PM_{10} Chronic cough OR 11.4 (2.8, 45.5) Bronchitis OR 23.2 (2.8, 45.5) Wheeze OR 1.41 (0.55, 3.58)
Zemp et al. (1999) 8 study sites in Switzerland. Pollutants: TSP, PM_{10}, SO_2, NO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 $\mu g/m^3$ with a mean of 21.	Logistic regression analysis of associations between prevalences of respiratory symptoms in random sample of adults and air pollution. Regressions adjusted for age, BMI, gender, parental asthma, education, and foreign citizenship.	Chronic cough and chronic phlegm and breathlessness were related to TSP, PM_{10} and NO_2.	Chronic cough, chronic phlegm and breathlessness were related to PM_{10}, and TSP.

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Heinrich et al. (1999) Bitterfeld, Zerbstand Hettstedt areas of former East Germany, During Sept. 1992 to July 1993 TSP ranged from 44 to 65 $\mu g/m^3$; PM_{10} measured October 1993 - March 1994 ranged from 33 to 40; and BS ranged from 26 to 42 $\mu g/m^3$. PM was measured with a Harvard impactor.	Parents of 2470 school children (5-14 yr) completed respiratory health questionnaire. Children excluded from analysis if had lived < 2 years in their current home, yielding an analysis group of 2,335 children. Outcomes studied: physician diagnosis for asthma, bronchitis, symptom, bronchial reactivity, skin prick test, specific IgE. Multiple logistic regression analyses examined regional effects.	Controlling for medical, socio-demographic, and indoor factors, children in more polluted area had circa 50% increase for bronchitic symptoms and physician-diagnosed allergies compared to control area and circa twice the respiratory symptoms (wheeze, shortness of breath and cough). Pulmonary function tests suggested slightly increased airway reactivity to cold for children in polluted area.	No single pollutant could be separated out as being responsible for poor respiratory health.
Heinrich et al. (2000) Three areas of former E. Germany Pollution measures: SO_2, TSP, and some limited PM_{10} data. TSP decreased from 65, 48, and 44 $\mu g/m^3$ to 43, 39, and 36 $\mu g/m^3$ in the three areas. PM was measured with a Harvard impactor.	Cross-sectional study of children (5-14 yr). Survey conducted twice, in 1992-1993 and 1995-1996; 2335 children surveyed in first round, and 2536 in second round. Only 971 children appeared in both surveys. The frequency of bronchitis, otitus media, frequent colds, febrile infections studied. Because changes measured over time in same areas, covariate adjustments not necessary.	PM and SO_2 levels both decreased in the same areas; so results are confounded.	The prevalence of all respiratory symptoms decreased significantly in all three areas over time.
Krämer et al. (1999) Six East and West Germany communities (Leipzig, Halle, Maddeburg, Altmark, Duisburg, Borken) Between 1991 and 1995 TSP levels in six communities ranged from 46 to 102 $\mu g/m^3$. Each East Germany community had decrease in TSP between 1991 and 1995. TSP was measured using a low volume sampler.	The study assessed relationship between TSP and airway disease and allergies by parental questionnaires in yearly surveys of children (5-8 yr) between February and May. The questions included pneumonia, bronchitis ever diagnosed by physician, number of colds, frequent cough, allergic symptoms. In all, 19,090 children participated. Average response was 87%. Analyses were conducted on 14,144 children for whom information on all covariates were available. Variables included gender; parent education, heating fuel, ETS. Logistic regression used to allow for time trends and SO_2 and TSP effects. Regression coefficients were converted to odds ratios.	TSP and SO_2 simultaneously included in the model. Bronchitis ever diagnosed showed a significant association. A decrease in raw percentage was seen between the start of the study and the end for bronchitis. Bronchitis seemed to be associated only with TSP in spite of huge differences in mean SO_2 levels.	Bronchitis ever diagnosed TSP per 50 $\mu g/m^3$ OR 1.63 CI (1.37 – 1.93) Halle (East) % TSP $\mu g/m^3$ Bronchitis 1991 102 60.5 1992 73 54.7 1993 62 49.6 1994 52 50.4 1995 46 51.9

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Baldi et al. (1999) 24 areas of seven French towns 1974-1976 Pollutants: TSP, BS, and SO_2, NO_4 3-year average TSP-mean annual values ranging 45-243 $\mu g/m^3$. TSP was measured by the gravimetric method.	Reanalysis of Pollution Atmospheric of Affection Respiratory Chroniques (PAARC) survey data to search for relationships between mean annual air pollutant levels and prevalence of asthma in 1291 adult (25-59 yrs) and 195 children (5-9 yrs) asthmatics. Random effects logistic regression model used and included age, smoking, and education level in the final model.	Only an association between SO_2 and asthma in adults observed. No other pollutant was associated. Nor was relationship with children seen. Meteorological variables and O_3 not evaluated.	For a 50 $\mu g/m^3$ increase in TSP Adult asthma prevalence OR 1.01 CI 0.92−1.11 SO_2 Adult asthma prevalence OR 1.26 CI 1.04−1.53
Zeghnoun et al. (1999) La Havre, France during 1993 and 1996. Daily mean BS levels measured in three stations ranged 12 - 14 $\mu g/m^3$.	Respiratory drug sales for mucolytic and anticough medications (most prescribed by a physician) were evaluated versus BS, SO_2, and NO_2 levels. An autoregressive Poisson regression model permitting overdispersion control was used in the analysis.	Respiratory drug sales associated with BS, NO_2, and SO_2 levels. Both an early response (0 to 3 day lag) and a longer one (lags of 6 and 9 days) were associated.	—
Leonardi et al. (2000) 17 cities of Central Europe Yearly average concentration (Nov. 1995 - Oct. 1996) across the 17 study areas varied from 41 to 96 $\mu g/m^3$ for PM_{10}, from 29 to 67 $\mu g/m^3$ for $PM_{2.5}$, and from 12 to 38 $\mu g/m^3$ for $PM_{10-2.5}$.	Cross-sectional study collected blood and serum samples from 10-61 school children aged 9 to 11 in each community 11 April to 10 May 1996. Blood and serum samples examined for parameters in relation to PM. Final analysis group of 366 examined for peripheral lymphocyte type and total immunoglobulin classes. Association between PM and each log transformed biomarker studied by linear regression in two-stage model with adjustment for confounding factors (age, gender, number of smokers in house, laboratory, and recent respiratory illness). This survey was conducted within the frame work of the Central European study of Air Quality and Respiratory Health (CEASAR) study.	Number of lymphocytes (B, $CD4^+$, $CD8^d$, and NK) increased with increasing concentration of PM adjusted for confounders. The adjusted regression slopes are largest and statistically significant for $PM_{2.5}$ as compared to PM_{10}, but small and non statistically signif. for $PM_{10-2.5}$. Positive relationship found between concentration of IgG in serum and $PM_{2.5}$ but not for PM_{10} or $PM_{10-2.5}$. Two other models produced similar outcomes: a multi-level linear regression model and an ordinal logistic regression model.	Adjusted Regression slope $PM_{2.5}$ $CD4^+$ 80% 95% CI (34; 143) p < 0.001 Total IgG 24% 95% CI (2; 52) p 0.034

**TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS:
RESPIRATORY SYMPTOM, LUNG FUNCTION**

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Turnovska and Kostiranev (1999) Dimitrovgrad, Bulgaria, May 1996 Total suspended particulate matter (TSPM) mean levels were $520 \pm I 61 \ \mu g/m^3$ in 1986 and $187 \pm 9 \ \mu g/m^3$ in 1996. SO_2, H_2S, and NO_2 also measured.	Respiratory function of 97 schoolchildren (mean age 10.4 ± 0.6 yr) measured in May 1996 as a sample of 12% of all four-graders in Dimitrovgrad. The obtained results were compared with reference values for Bulgarian children aged 7 to 14 yr, calculated in the same laboratory in 1986 and published (Gherghinova et al., 1989; Kostianev et al., 1994). Variation analysis technique were used to treat the data.	Vital capacity and FEV_1 were significantly lower (mean value. = 88.54% and 82.5% respectfully) comparing values between 1986 and 1996. TSPM pollution had decreased by 2.74 times to levels still higher than Bulgarian and WHO standards.	—
Jedrychowski et al. (1999) In Krakow, Poland in 1995 and 1997 Spacial distributions for BS and SO_2 derived from network of 17 air monitoring stations. BS 52.6 $\mu g/m \pm 53.98$ in high area and 33.23 ± 35.99 in low area.	Effects on lung function growth studied in preadolescent children. Lung function growth rate measured by gain in FVC and FEV_1 and occurrence of slow lung function growth (SLFG) over the 2 yr period defined as lowest quintile of the distribution of a given test in gender group. 1129 children age 9 participated in first year and 1001 in follow-up 2 years later. ATS standard questionnaire and PFT methods used. Initially univariate descriptive statistics of pulmonary function indices and SLFG were established, followed by multivariate linear regression analyses including gender, ETS, parental education, home heating system and mold. SO_2 also analyzed.	Statistically significant negative association between air pollution level and lung function growth (FVC and FEV_1) over the follow up in both gender groups. SLFG was significantly higher in the more polluted areas only among boys. In girls there was consistency in the direction of the effect, but not stat. significant. Could not separate BS and SO_2 effects on lung function growth. Excluding asthma subjects subsample (size 917) provided similar results.	Boys SLFG (FVC) OR = 2.15 (CI 1.25 – 3.69) SLFG (FEV_1) OR = 1.90 (CI 1.12 – 3.25) Girls FVC OR = 1.50 (CI 0.84 – 2.68) FEV1 OR = 1.39 (CI 0.78 – 2.44)
Jedrychowski and Flak (1998) In Kracow Poland, in 1991-1995 Daily 24 h concentration of SPM (black smoke) measured at 17 air monitoring stations. High areas had 52.6 $\mu g/m^3$ mean compared to low areas at 33.2 $\mu g/m^3$.	Respiratory health survey of 1,129 school children (aged 9 yr). Respiratory outcomes included chronic cough, chronic phlegm, wheezing, difficulty breathing and asthma. Multi-variable logistic regression used to calculate prevalence OR for symptoms adjusted for potential confounding.	The comparison of adjusted effect estimates revealed chronic phlegm as unique symptom related neither to allergy nor to indoor variable but was associated significantly with outdoor air pollution category (APL). No potential confounding variable had major effect.	It was not possible to assess separately the contribution of the different sources of air pollutants to the occurrence of respiratory symptoms. ETS and household heating (coal vs. gas vs. central heating) appeared to be of minimal importance.

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Latin America			
Calderón-Garcidueñas et al. (2000) Southwest Metropolitan Mexico City (SWMMC) winter of 1997 and summer of 1998.	Study of 59 SWMMC children to evaluate relationship between exposure to ambient pollutants (O_3 and PM_{10}) and chest x-ray abnormalities. Fishers exact test used to determine significance in a 2x2 task between hyperinflation and exposure to SWMMC pollutant atmosphere and to control, low-pollutant city atmosphere.	Bilateral symmetric mild lung hyperinflation was significantly associated with exposure to the SWMMC air pollution mixture ($p>0.0004$). This raises concern for development of chronic disease outcome in developing lungs.	—
Australia			
Lewis et al. (1998) Summary measures of PM_{10} and SO_2 estimated for each of 10 areas in steel cities of New South Wales. PM_{10} was measured using a high volume sampler with size-selective inlets.	Cross-sectional survey of children's health and home environment between Oct 1993 and Dec 1993 evaluated frequency of respiratory symptoms (night cough, chest colds, wheeze, and diagnosed asthma). Covariates included parental education and smoking, unflued gas heating, indoor cats, age, sex, and maternal allergy. Logistic regression analysis used allowing for clustering by GEE methods.	SO_2 was not related to differences in symptom rates, but adult indoor smoking was.	Night cough OR 1.34 (1.18, 1.53) Chest colds OR 1.43 (1.12, 1.82) Wheeze OR 1.13 (0.93, 1.38)
Asia			
Wong et al. (1999) Hong Kong, 1989 to 1991 Sulfate concentrations in respirable particles fell by 38% after implementing legislation reducing fuel sulfur levels.	3405 nonsmoking, women (mean age 36.5 yr; SD ± 3.0) in a polluted district and a less polluted district were studied for six respiratory symptoms via self-completed questionnaires. Binary latent variable modeling used.	Comparison was by district; no PM measurements reported. Results suggest control regulation may have had some (but not statistically significant) impact.	—

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Wang et al. (1999) Kaohsiung and Panting, Taiwan October 1995 to June 1996 TSP measured at 11 stations, PM_{10} at 16 stations. PM_{10} annual mean ranged from 19.4 to 112.81 $\mu g/m^3$ (median = 91.00 $\mu g/m^3$) TSP ranged from 112.81 to 237.82 $\mu g/m^3$ (median = 181.00). CO, NO_2, SO_2, hydrocarbons and O_3 also measured.	Relationship between asthma and air pollution examined in cross-sectional study among 165,173 high school students (11-16 yr). Evaluated wheeze, cough and asthma diagnosed by doctor. Video determined if student displayed signs of asthma. Only 155,283 students met all requirements for study analyses and, of these, 117,080 were covered by air monitoring stations. Multiple logistic regression analysis used to determine independent effects of risk factors for asthma after adjusting for age, gender, ETS, parents education, area resident, and home incense use.	Asthma significantly related to high levels of TSP, NO_2, CO, O_3 and airborne dust. However PM_{10} and SO_2 not associated with asthma. The lifetime prevalence of asthma was 18.5% and the 1-year prevalence was 12.5%.	Adjusted OR PM_{10} 1.00 (0.96‒1.05) TSP 1.29 (1.24‒1.34)
Guo et al. (1999) Taiwan, October 1955 and May 1996 PM_{10} measured by beta-gauge. Also monitoring for SO_2, NO_2, O_3, CO. PM_{10} ranged from 40 to 110 $\mu g/m^3$ with a mean of 69.	Study of asthma prevalence and air pollutants. Survey for respiratory disease and symptoms in middle-school students age < 13 to ≥ 15 yr. Total of 1,018,031 (89.3%) students and their parents responded satisfactorily to the questionnaire. Schools located with 2 km of 55 monitoring sites. Logistic regression analysis conducted, controlling for age, hx eczema, parents education.	Because of close correlation among air pollutants, not possible to separate effects of individual ones. Factor analysis used to group into two classes (traffic-related and stationary fossil fuel-related). No association found between lifetime asthma prevalence and nontraffic related air pollutants (SO_2, PM_{10}).	—
Wang et al. (1999) Chongquing, China April to July 1995 Dichot samplers used to measure $PM_{2.5}$. Mean $PM_{2.5}$ level high in both urban (143 $\mu g/m^3$) and suburban (139 $\mu g/m^3$) area. SO_2 also measured	Study examined relationship between PFT and air pollution. Pulmonary function testing performed on 1,075 adults (35 - 60 yr) who had never smoked and did not use coal stoves for cooking. Generalized additive model used to estimate difference, between two areas for FEV_1, FVC, and $FEV_1/FVC\%$ with adjustment for confounding factors (gender; age, height, education, passive smoking, and occupational exposures).	Mean SO_2 concentration in the urban and suburban area highly statistically significant different (213 and 103 $\mu g/m^3$ respectfully). $PM_{2.5}$ difference was small, while levels high in both areas. Estimated effects on FEV1 statistically different between the two areas.	Difference between urban and suburban area excluding occupational exposures: FEV_1 / FVC B ‒ 119.79 / B ‒ 57.89 SE 28.17 / SE 30.80 t ‒ 4.25 / t ‒ 1.88 p < 0.01 / p < 0.05

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Zhang et al. (1999) 4 areas of 3 Chinese Cities (1985 - 1988) TSP levels ranged from an annual arithmetic mean 137 μg/m^3 to 1250 μg/m^3 using gravimetric methods.	A pilot study of 4 districts of 3 Chinese cities in for the years 1985-1988, TSP levels and respiratory health outcomes studied. 4,108 adults (< 49 yrs) examined by questionnaires for couth, phlegm, wheeze, asthma, and bronchitis. Categorical logistic—regression model used to calculate odds ratio. SO$_2$ and NO$_2$ were also examined. Other potential confounding factors (age, education level, indoor ventilation, and occupation) examined in the multiple logistic regression model.	Results suggested that the OR's for cough, phlegm, persistent cough and phlegm and wheeze increased as outdoor TSP concentrations did. .	Wheeze produced largest OR for both mothers and fathers in all locations.
Qian et al. (2000) 4 China cities The 4 year average TSP means were 191, 296, 406, and 1067 μg/m^3. SO$_2$ and NO$_2$ measurements were also available. TSP was measured gavimetrically.	Pilot cross-sectional survey of 2789 elementary school children in four Chinese communities chosen for their PM gradient. Frequency of respiratory symptoms (cough, phlegm, wheeze, and diagnosed asthma, bronchitis, or pneumonia) assessed by questionnaire. Covariates included parental occupation, education and smoking. The analysis used logistic regression, controlling for age, sex, parental smoking, use of coal in home, and home ventilation.	Results not directly related to pollution levels, but symptom rates were highest in highest pollution area for cough, phlegm, hospitalization for respiratory disease, bronchitis, and pneumonia. No gradient correlating with pollution levels found for the three lower exposure communities.	—

9. INTEGRATIVE SYNTHESIS

9.1 INTRODUCTION

This chapter focuses on integration of key information on exposure-dose-response risk assessment components drawn from the preceding detailed chapters, to provide a coherent framework for assessment of human health risks posed by ambient particulate matter (PM) in the United States. As such, the chapter updates the integrated assessment of available scientific information regarding ambient PM sources, exposures, and health risks as they pertain to the United States that was provided in the 1996 Particulate Matter Air Quality Criteria Document (1996 PM AQCD; U.S. Environmental Protection Agency, 1996a).

This chapter mainly uses the 10 Questions from the National Research Council (NRC) Particulate Matter (PM) Research Agenda (NRC, 1998, 2001) as an organizing principle to summarize and integrate key points derived from the material presented in detail in Chapters 1 to 8 of this document. After providing certain background information, the chapter is then basically organized to follow the Risk Assessment Framework (as shown in Figure 9-1), and it addresses the NRC questions noted earlier in Chapter 1 within the context of discussing general topic areas that follow the flow of that framework from sources/emissions to effects. Some additional topics in addition to the 10 NRC questions are also addressed.

Unlike the other criteria pollutants (O_3, CO, NO_2, SO_2, and Pb), PM is not a specific chemical entity but is a mixture of particles of different sizes, compositions, and properties. Therefore, it is useful to present some background on the size, chemistry and physics of PM before entering the Risk Assessment Framework. Thus, this chapter first provides background information on key features of atmospheric particles, highlighting important distinctions between fine- and coarse-mode particles with regard to size, chemical composition, sources, atmospheric behavior, and potential human exposure relationships—distinctions that collectively continue to suggest that fine- and coarse-mode particles should be treated as two distinct subclasses of air pollutants. Recent trends in U.S. concentrations of different ambient PM size and composition fractions (e.g., PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) and ranges of variability seen in U.S. regions and urban airsheds are also summarized to place the ensuing human exposure and health effects discussions
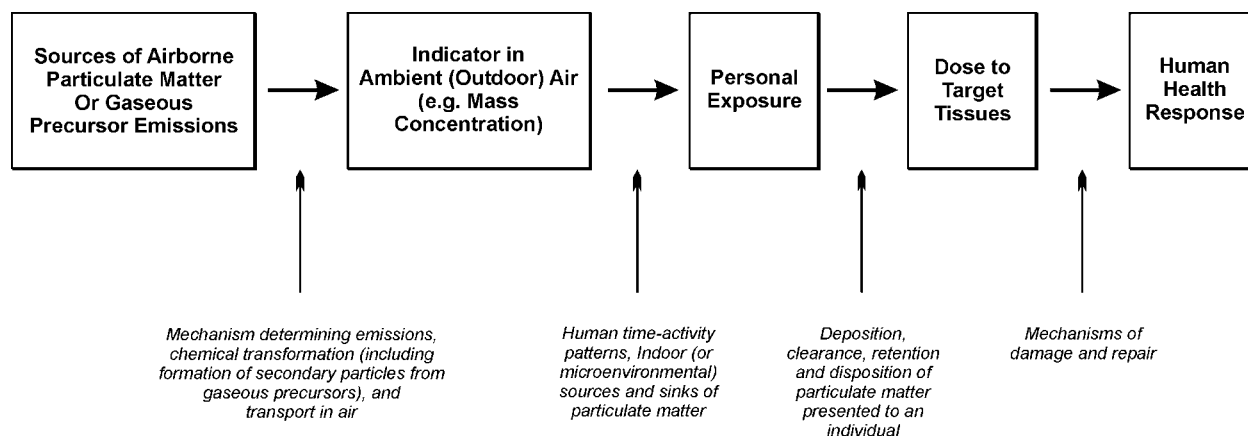
Figure 9-1. A general framework for integrating particulate-matter research. Note that this figure is not intended to represent a framework for research management. Such a framework would include multiple pathways for the flow of information.

Source: National Research Council (2001), as modified from NRC (1983, 1994), Lioy (1990), and Sexton et al. (1992).

1 in perspective. After discussing human exposure aspects, the chapter next summarizes key points

2 regarding respiratory tract dosimetry, followed by a discussion of the extensive PM health

3 database that has expanded greatly during recent years. The latter includes numerous new

4 epidemiologic studies of populations throughout the world published since the 1996 PM AQCD

5 that provide further evidence that serious health effects (mortality, exacerbation of chronic

6 disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of

7 PM found in contemporary U.S. urban air sheds. Evaluations of other possible explanations for

8 the reported PM epidemiology results (e.g., other co-pollutants, choice of models, etc.) also are

9 discussed, ultimately leading to the conclusion that the reported associations of PM exposure and

10 effects are valid.

11   New toxicologic evidence (derived from controlled exposure studies of humans and

12 laboratory animals) is also discussed, which elucidates likely mechanisms of action and other

13 information that greatly enhances the plausibility of the epidemiologic findings in comparison to

14 1996. Quantitative evidence is then discussed that (a) further substantiates associations of such

15 serious health effects with U.S. ambient PM_{10} levels, (b) also more strongly establishes fine

1 particles (as indexed by various indicators, e.g., $PM_{2.5}$) as likely being important contributors to

2 the observed human health effects, and (c) now provides additional information on associations

3 between coarse-fraction ($PM_{10-2.5}$) particles and adverse health impacts. The overall coherence of

4 the newer epidemiologic database also is discussed, which strengthens the 1996 PM AQCD

5 evaluation suggesting a likely causal role of ambient PM in contributing to the reported effects.

6   The nature of the observed effects and the biological mechanisms that might underlie such

7 effects then are discussed. The discussion of potential mechanisms of injury examines ways in

8 which PM could induce health effects. The increased, but still limited, availability of new

9 experimental evidence necessary to evaluate or directly substantiate the viability of hypothesized

10 mechanisms is noted. Information concerning possible contributions of particular classes of

11 specific ambient PM constituents also is summarized.

12   The chapter also provides information on the identification of susceptible population

13 groups at special risk for ambient PM effects and factors placing them at increased risk, which

14 need to be considered in generating risk estimates for the possible occurrence of PM-related

15 health events in the United States.

16

17

18 ## 9.2 BACKGROUND

19 ### 9.2.1 Basic Concepts

20   Atmospheric particles originate from a variety of sources and possess a range of

21 morphological, chemical, physical, and thermodynamic properties. Sources include combustion,

22 photochemical oxidation of precursors, and soil dust. Atmospheric particles contain inorganic

23 ions, metallic compounds, elemental carbon, organic compounds, and crustal compounds. Some

24 atmospheric particles are hygroscopic and contain particle-bound water. The organic fraction is

25 especially complex, containing hundreds of organic compounds. Individual particles may be

26 composed by any number of the above and other components.

27

28 ### 9.2.2 Particle Size Distributions

29   As discussed in Chapter 2, the distribution of particles with respect to size is an important

30 physical parameter governing their behavior. Atmospheric particles vary in density and often are

1   not spherical. Therefore, their diameters are often described by an "equivalent" diameter (i.e.,

2   that of a unit density sphere that would have the same physical behavior). The aerodynamic

3   diameter (D_a) depends on the density of the particle and is defined as the diameter of a spherical

4   particle with a density of 1 g/cm^3 but with a settling velocity equal to that of the particle in

5   question. The atmospheric deposition rates of particles, and therefore, their residence times in

6   the atmosphere, are a strong function of their aerodynamic diameters. The aerodynamic diameter

7   also influences deposition patterns of particles within the lung. The effects of atmospheric

8   particles on visibility, radiative balance, and climate, will also be influenced by the size

9   distribution of the particles. Atmospheric particles cover several orders of magnitude in particle

10 size. Therefore, size distributions often are expressed in terms of the logarithm of the particle

11 diameter on the X-axis and the measured differential concentration on the Y-axis. If the

12 differential concentration is plotted on a linear scale, the number of particles (per cm^3 of air), or

13 the surface area, the volume, or the mass of particles (per m^3 of air) having diameters in the size

14 range from log D to log(D + ΔD), will be proportional to the area under that part of the size

15 distribution curve.

16   Averaged atmospheric size distributions are shown in Figure 9-2. Figure 9-2a shows the

17 number distributions of particles, on a logarithmic scale, as a function of particle diameter for

18 several aerosols. The particle volume distributions for two of these are shown in Figure 9-2b.

19 These distributions show that most of the particles are quite small, below 0.1 μm; whereas most

20 of the particle volume (and therefore most of the mass) is found in particles larger than 0.1 μm.

21

22 **9.2.3 Definitions of Particle Size Fractions**

23   Aerosol scientists use four different approaches or conventions in the classification of

24 particles by size: (1) modes, based on the observed size distributions and formation mechanisms;

25 (2) cut point, usually based on the 50% cut point of the specific sampling device; (3) dosimetry

26 or occupational health sizes, based on the entrance into various compartments of the respiratory

27 system; and (4) legally specified, regulatory sizes for air quality standards.

28

29   ***Modal***. The modal classification, first proposed by Whitby (1978), is shown in Figure 9-3.

30 In polluted atmospheres, the nuclei mode can be seen clearly in the volume distribution only in

31 traffic or near traffic or other sources of nuclei mode particles. The observed modal structure is
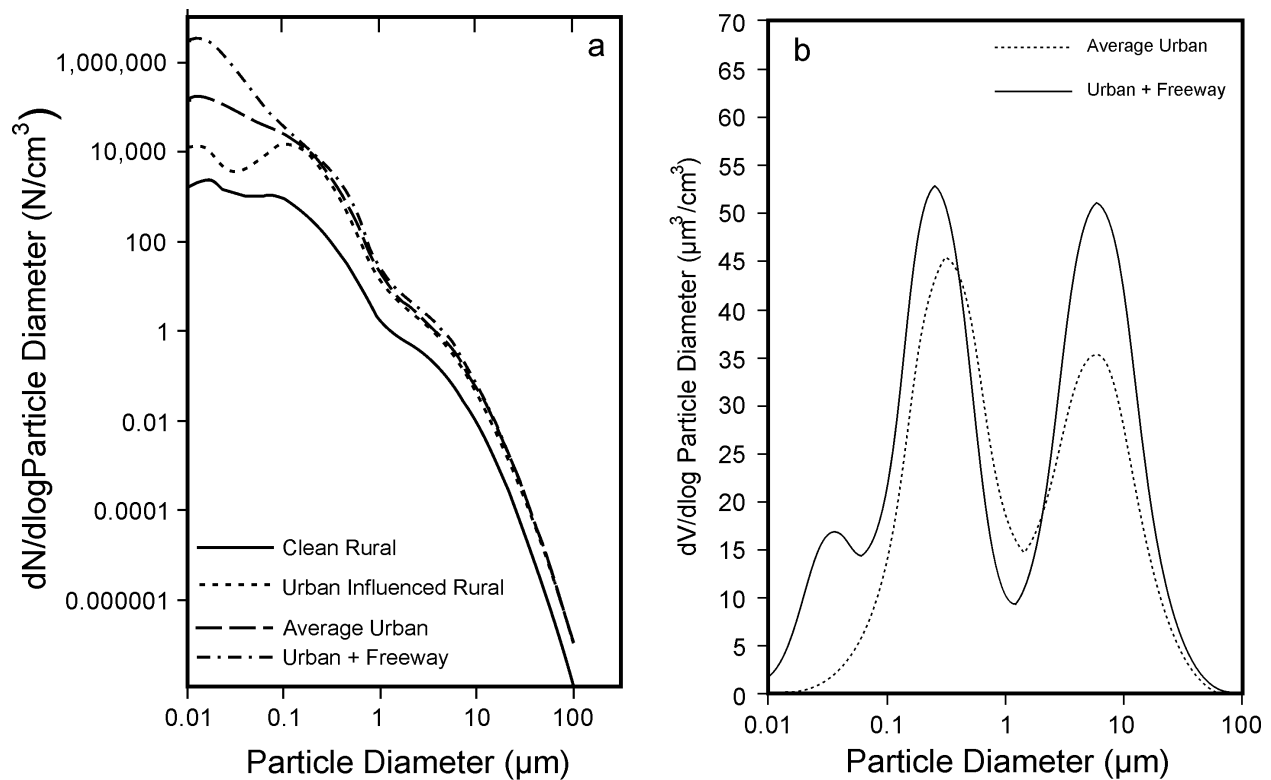
Figure 9-2. **Particle size distributions: (a) number of particles as a function of particle diameter: number concentrations are shown on a logarithmic scale to display the wide range by site and size and (b) particle volume as a function of particle diameter: for the averaged urban and freeway-influenced urban number distributions shown in Figure 2-1 of Chapter 2.**

Source: Whitby and Sverdrup (1980).

1   frequently approximated by several log-normal distributions. Terms used in the modal

2   description of particle size distributions are defined as follows. *Coarse Mode:* The distribution

3   of particles with diameters mostly greater than the minimum in the particle mass or volume

4   distributions, which generally occurs between 1 and 3 μm. These particles are usually

5   mechanically generated (e.g., from wind erosion of crustal material). *Fine Mode:* The

6   distribution of particles with diameters mostly smaller than the minimum in the particle mass or

7   volume distributions, which generally occurs between 1 and 3 μm. These particles are generated

8   in combustion or formed from gases. The fine mode includes the accumulation mode and the

9   nuclei mode. *Nuclei Mode*: That portion of the fine particle mode with diameters below about
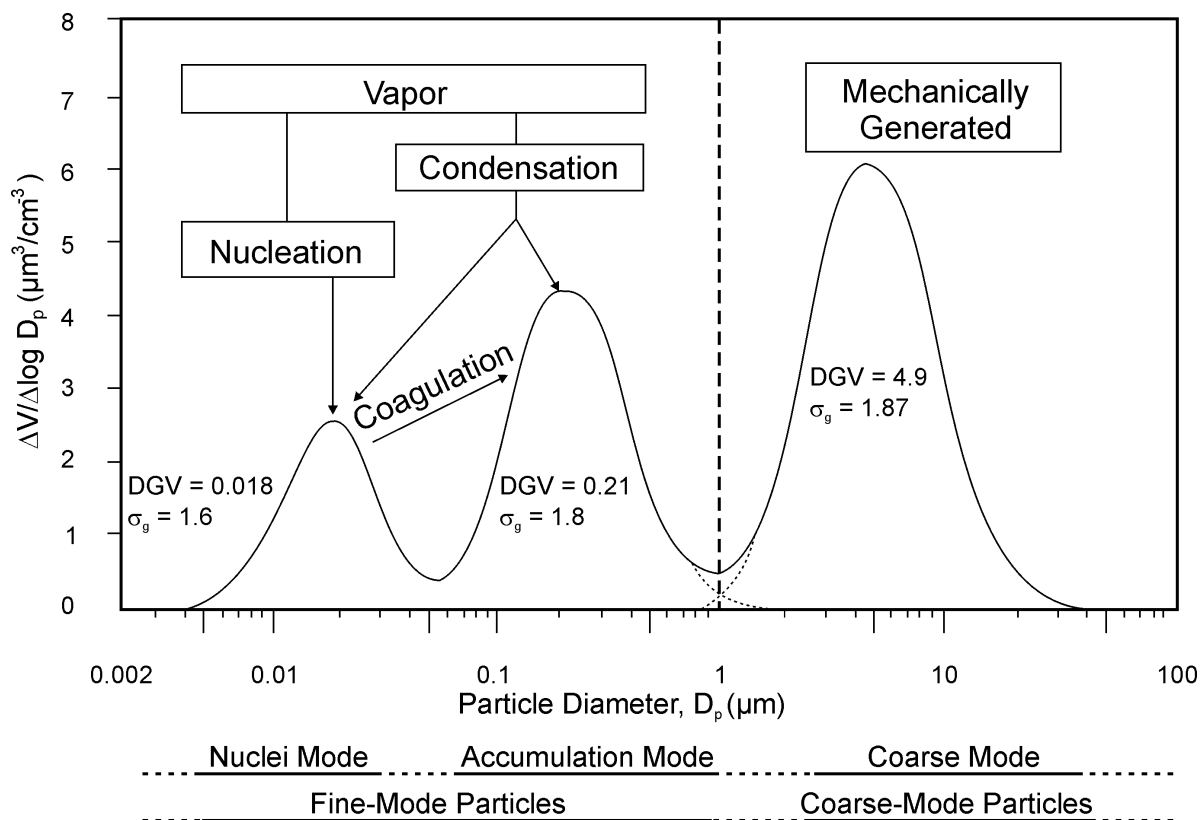
Figure 9-3. Volume size distribution, measured in traffic, showing fine-mode and coarse-mode particles and the nuclei and accumulation modes within the fine-particle mode. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and σ_g (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).

Source: Adapted from Wilson and Suh (1997).

1 0.1 μm. Toxicologists and epidemiologists use the term "ultrafine" and aerosol physicists and

2 material scientists use the term "nanoparticles" to refer to particles in the nuclei-mode size range.

3 *Accumulation Mode*: That portion of the fine particle mode with diameters above about 0.1 μm.

4   The major processes that influence the formation and growth of particles in the three modes

5 are also shown in Figure 9-3. New particles may be formed by nucleation from gas phase

6 material. Particles may grow by condensation as gas phase material condenses on existing

7 particles. Particles also may grow by coagulation as two particles combine to form one. Gas

1   phase material condenses preferentially on smaller particles, and the rate constant for coagulation

2   of two particles decreases as the particle size increases. Therefore, nuclei mode particles grow

3   into the accumulation mode, but accumulation mode particles do not normally grow into the

4   coarse mode.

5   Over the years, the terms fine and coarse, as applied to particle sizes, have lost the precise

6   meaning given in Whitby's (1978) definition. In any given article, therefore, the meaning of fine

7   and coarse, unless defined, must be inferred from the author's usage. In particular, $PM_{2.5}$ and

8   fine-mode particles are not equivalent. In this document, the term "mode" is used with fine and

9   coarse when it is desired to specify the distribution of fine-mode particles or coarse-mode

10   particles as shown in Figure 9-3.

11

12   ***Size-Selective and Occupational Health Size Fractions***

13   Size-selective sampling refers to the collection of particles below or within a specified

14   aerodynamic size range, usually defined by the upper 50% cut point size, and has arisen in an

15   effort to measure particle size fractions with some special significance (e.g., health, visibility,

16   source apportionment, etc.). An example of a PM_{10} and a $PM_{2.5}$ size cut are shown in Figure 9-4.

17   The subscripts, 10 and the 2.5, signify the 50% cut size, i.e., the size at which 50% of the

18   particles are collected and 50% of the particles are rejected. As can be seen, the cut is not

19   perfectly sharp. Some particles larger than the 50% cut point are collected; neither are all

20   particles smaller than the 50% cut point collected.

21   The occupational health community has defined size fractions for use in the protection of

22   human health. This convention classifies particles into inhalable, thoracic, and respirable

23   particles according to their upper size cuts (also shown in Figure 9-4). However, these size

24   fractions may also be characterized in terms of their entrance into various compartments of the

25   respiratory system. Thus, inhalable particles enter the respiratory tract, including the head

26   airways. Thoracic particles travel past the larynx and reach the lung airways and the

27   gas-exchange regions of the lung. Respirable particles are a subset of thoracic particles that are

28   more likely to reach the gas-exchange region of the lung.

29

30   ***Regulatory Size Cuts***. In 1987, the NAAQS for PM were revised to use PM_{10}, rather than

31   total suspended particulate matter (TSP), as the indicator for the NAAQS for PM (Federal
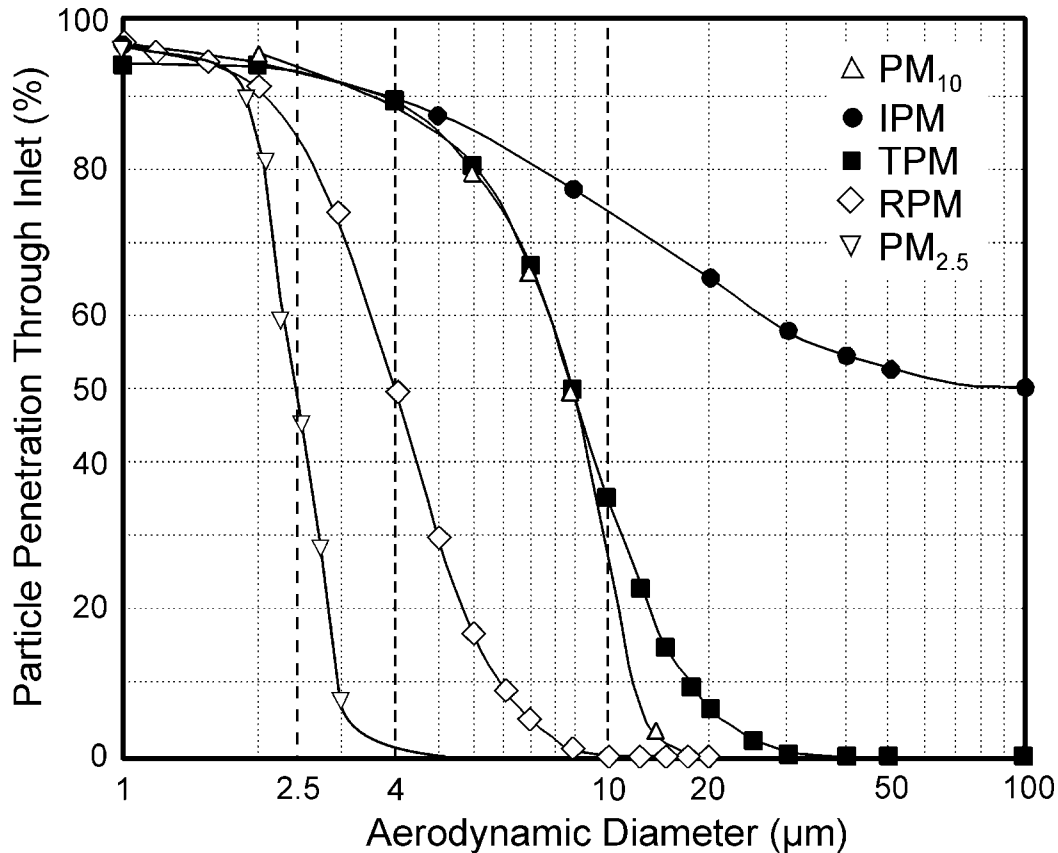
Figure 9-4. **Specified particle penetration (size-cut curves) through an ideal (no-particle-loss) inlet for five different size-selective sampling criteria. Regulatory size cuts are defined in the Code of Federal Regulations; $PM_{2.5}$ (2001a), PM_{10} (2001b). $PM_{2.5}$ is also defined in the Federal Register (1997). Size-cut curves for inhalable particulate matter (IPM), thoracic particulate matter (TPM) and respirable particulate matter (RPM) size cuts are computed from definitions given by American Conference of Governmental and Industrial Hygienists (1994).**

1   Register, 1987). The use of PM_{10} as an indicator is an example of size-selective sampling based

2   on a regulatory size cut (Federal Register, 1987). The selection of PM_{10} as an indicator was

3   based on health considerations and was intended to focus regulatory concern on those particles

4   small enough to enter the thoracic region of the human respiratory tract. The $PM_{2.5}$ standard set

5   in 1997 is also an example of size-selective sampling based on a regulatory size cut (Federal

6   Register, 1997). The $PM_{2.5}$ standard was based primarily on epidemiological studies using

7   concentrations measured with $PM_{2.5}$ samplers as an exposure index. However, the $PM_{2.5}$ sampler

1   was not designed to collect respirable particles. It was designed to collect fine-mode particles.

2   EPA is currently considering the possibility of a thoracic coarse particle standard with $PM_{10-2.5}$ as

3   an indicator. Examples of regulatory size cuts are shown in Figure 9-5. Note also that, in the

4   range of particle aerodynamic diameter (D_a) between 1.0 and 2.5 μm, there is overlap between

5   fine- and coarse-mode particles. The degree of overlap depends on prevailing conditions of

6   humidity and the amount of soil dust in the atmosphere.

7

8
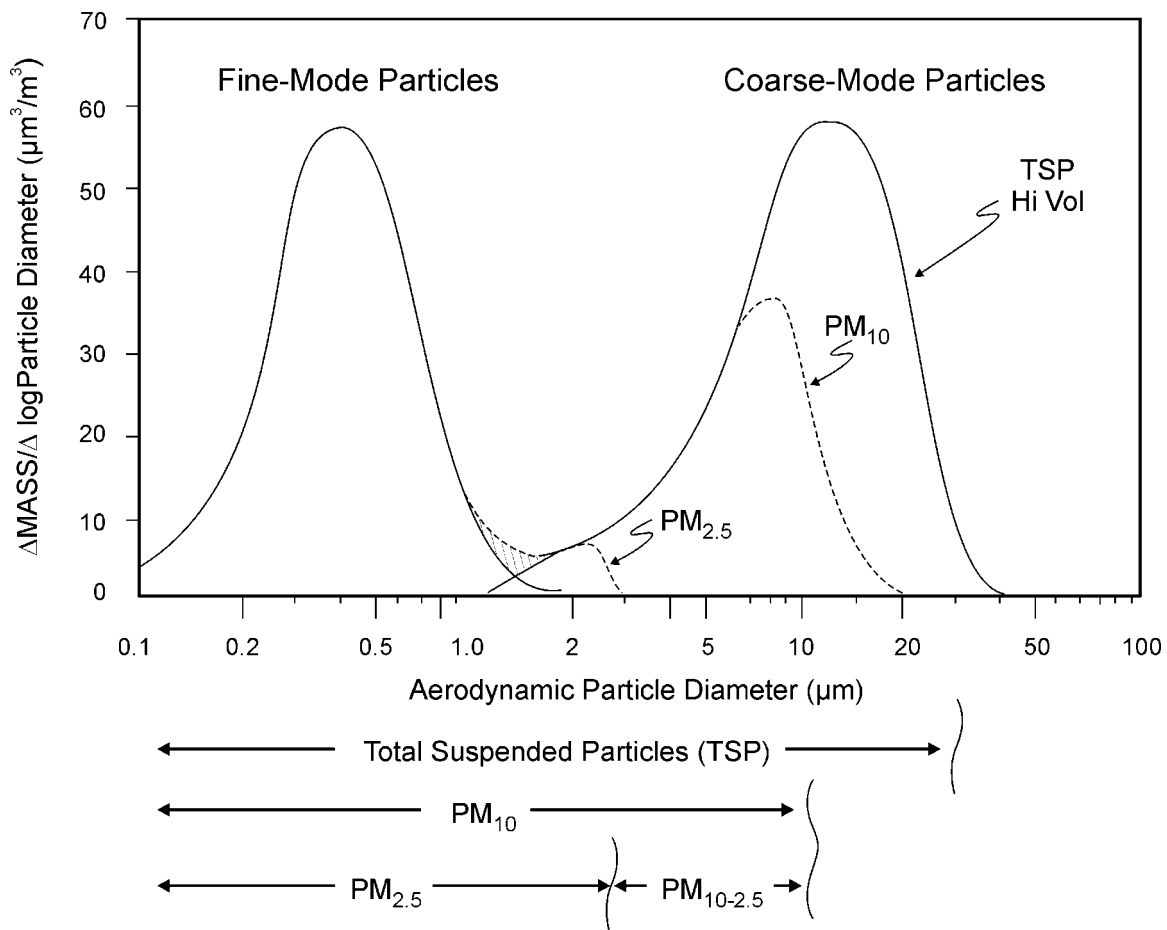
Figure 9-5. **An idealized distribution of ambient particulate matter showing fine-mode particles and coarse-mode particles and the fractions collected by size-selective samplers. (WRAC is the Wide Range Aerosol Classifier which collects the entire coarse mode [Lundgren and Burton, 1995].)**

Source: Adapted from Wilson and Suh (1997).

9.3 CHARACTERIZATION OF EMISSION SOURCES

What are the size distribution, chemical composition, and mass-emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary particle formation through atmospheric chemical reactions?

The linkages between airborne PM and its sources are not as well defined as they are for many other pollutants. In large part this is because PM is not a well defined chemical entity but represents a complex mixture of primary and secondary components. PM is called "primary" if it is in the same chemical form in which it was emitted into the atmosphere. PM is called "secondary" if it is formed by chemical reactions in the atmosphere. Primary coarse particles are usually formed by mechanical processes, such as the abrasion of surfaces or by the suspension of soil or biological material. This includes material emitted in particulate form, such as wind-blown dust, sea salt, road dust, and combustion-generated particles such as fly ash and soot. $PM_{10-2.5}$ is mainly primary in origin. Primary fine particles are emitted from sources either directly as particles or as vapors that rapidly condense to form ultrafine or nuclei-mode particles. Secondary PM is formed by chemical reactions of free, adsorbed, or dissolved gases. Most secondary fine PM is formed from condensable vapors generated by chemical reactions of gas-phase precursors. Secondary formation processes can result in either the formation of new particles or the addition of condensable vapor to preexisting particles. Most of the sulfate and nitrate and a portion of the organic compounds in atmospheric particles are formed by chemical reactions in the atmosphere. Because precursor gases undergo mixing during transport from their sources, it is difficult to identify individual sources of secondary constituents of PM.

Table 9-1 summarizes anthropogenic and natural sources for the major primary and secondary aerosol constituents of fine and coarse particles. Anthropogenic sources can be further divided into stationary and mobile sources. Stationary sources include fuel combustion for electrical utilities, residential space heating and industrial processes; construction and demolition; metals, minerals, and petrochemicals; wood products processing; mills and elevators used in agriculture; erosion from tilled lands; waste disposal and recycling; and fugitive dust from paved and unpaved roads. Mobile, or transportation-related, sources include direct emissions of primary PM and secondary PM precursors from highway and off-highway vehicles

TABLE 9-1. CONSTITUENTS OF ATMOSPHERIC PARTICLES AND THEIR MAJOR SOURCES[1]

Aerosol species	Primary (PM <2.5 μm)		Primary (PM >2.5 μm)		Secondary PM Precursors (PM <2.5 μm)	
	Natural	Anthropogenic	Natural	Anthropogenic	Natural	Anthropogenic
$SO_4^=$ Sulfate	Sea spray	Fossil fuel combustion	Sea spray	—	Oxidation of reduced sulfur gases emitted by the oceans and wetlands and SO_2 and H_2S emitted by volcanism and forest fires	Oxidation of SO_2 emitted from fossil fuel combustion
NO_3^- Nitrate	—	—	—	—	Oxidation of NO_x produced by soils, forest fires, and lighting	Oxidation of NO_x emitted from fossil fuel combustion and in motor vehicle exhaust
Minerals	Erosion and re-entrainment	Fugitive dust paved and unpaved roads, agriculture, and forestry	Erosion and re-entrainment	Fugitive dust, paved and unpaved road dust, agriculture, and forestry	—	—
NH_4^+ Ammonium	—	—	—	—	Emissions of NH_3 from wild animals, and undisturbed soil	Emissions of NH_3 from animal husbandry, sewage, and fertilized land
Organic carbon (OC)	Wild fires	Prescribed burning, wood burning, motor vehicle exhaust, and cooking	—	Tire and asphalt wear and paved road dust	Oxidation of hydrocarbons emitted by vegetation (terpenes, waxes) and wild fires	Oxidation of hydrocarbons emitted by motor vehicles, prescribed burning, and wood burning
Elemental carbon (EC)	Wild fires	Motor vehicle exhaust, wood burning, and cooking	—	Tire and asphalt wear and paved road dust	—	—
Metals	Volcanic activity	Fossil fuel combustion, smelting, and brake wear	Erosion, re-entrainment, and organic debris	—	—	—
Bioaerosols	Viruses and bacteria	—	Plant and insect fragments, pollen, fungal spores, and bacterial agglomerates	—	—	—

[1]Dash (–) indicates either very minor source or no known source of component.

1   and nonroad sources. In addition to fossil fuel combustion, biomass in the form of wood is

2   burned for fuel. Vegetation is burned to clear new land for agriculture and for building

3   construction, to dispose of agricultural and domestic waste, to control the growth of animal or

4   plant pests, and to manage forest resources (prescribed burning). Also shown are sources for

5   precursor gases whose oxidation forms secondary particulate matter.

6   In general, the sources of fine PM are very different from those for coarse PM. Some of the

7   mass in the fine size fraction has been formed during combustion from material that volatilized

8   in combustion chambers and then recondensed before emission into the atmosphere. By and

9   large, however, most ambient $PM_{2.5}$ is secondary, having been formed in the atmosphere from

10   photochemical reactions involving precursor gases. Transport and transformations of precursors

11   can occur over distances of hundreds of kilometers. The coarse PM constituents have shorter

12   lifetimes in the atmosphere, so their effects tend to be more localized. Only major sources for

13   each constituent within each broad category shown at the top of Table 9-1 are listed. Not all

14   sources are equal in magnitude. Chemical characterizations of primary particulate emissions for

15   a wide variety of natural and anthropogenic sources (as shown in Table 9-1) were given in

16   Chapter 5 of the 1996 PM AQCD. Summary tables of the composition of source emissions

17   presented in the 1996 PM AQCD and updates to that information are provided in Appendix 3D

18   of Chapter 3 in this document. The profiles of source composition are based largely on results of

19   various studies that collected signatures for use in source apportionment studies.

20   Natural sources of primary PM include windblown dust from undisturbed land, sea spray,

21   and plant and insect debris. The oxidation of a fraction of terpenes emitted by vegetation and

22   reduced sulfur species from anaerobic environments leads to secondary PM formation.

23   Ammonium (NH_4^+) ions, which play a major role in regulating the pH of particles, are derived

24   from emissions of ammonia (NH_3) gas. Source categories for NH_3 have been divided into

25   emissions from undisturbed soils (natural) and emissions that are related to human activities

26   (e.g., fertilized lands, domestic and farm animal waste). There is ongoing debate about

27   characterizing emissions from wild fires (i.e., unwanted fire) as either natural or anthropogenic.

28   Wildfires have been listed in Table 9-1 as natural in origin, but land management practices and

29   other human actions affect the occurrence and scope of wildfires. For example, fire suppression

30   practices allow the buildup of fire fuels and increase the susceptibility of forests to more severe

31   and infrequent fires from whatever cause, including lightning strikes. Similarly, prescribed

1 burning is listed as anthropogenic, but can viewed as a substitute for wildfires that would

2 otherwise eventually occur on the same land.

3   The precursors to secondary PM have natural and anthropogenic sources, just as primary

4 PM has natural and anthropogenic sources. Whereas the major atmospheric chemical

5 transformations leading to the formation of particulate nitrate and sulfate have been relatively

6 well studied, those involving the formation of secondary aerosol organic carbon are still under

7 active investigation. A large number of organic precursors are involved, many of the kinetic

8 details still need to be determined, and many of the actual products of the oxidation of

9 hydrocarbons have yet to be identified.

10   However, over the past decade, a significant amount of research has been carried out to

11 improve the understanding of the atmospheric chemistry of secondary organic PM (SOPM)

12 formation. Although additional sources of SOPM might still be identified, there appears to be a

13 general consensus that biogenic compounds (monoterpenes, sesquiterpenes) and aromatic

14 compounds (toluene, ethylbenzene) are the most significant SOPM precursors. A large number

15 of compounds have been detected in biogenic and aromatic SOPM, although the chemical

16 composition of these two categories has not been fully established, especially for aromatic

17 SOPM. Transformations that occur during the aging of particles are still not adequately

18 understood. There are still large gaps in current understanding of a number of key processes

19 relating to the partitioning of semivolatile compounds between the gas phase and ambient

20 particles containing organic compounds, liquid water, inorganic salts, and acids. In addition,

21 there is a general lack of reliable analytical methods for measuring multifunctional oxygenated

22 compounds in the gas and aerosol phases.

23   Emissions estimates for primary $PM_{2.5}$ components shown in Table 9-1 are provided in

24 Table 9-2 and emissions of precursors of secondary $PM_{2.5}$ are shown in Table 9-3. The values

25 shown are annual averages for the entire United States. As can be seen from a comparison of the

26 entries in the two tables, the emissions of precursor gases of secondary PM are much larger than

27 those for primary PM. It should be noted here that the emissions estimates given above are

28 subject to a considerable degree of uncertainty, which varies from species to species. In addition,

29 there can be a great deal of temporal variability in the emissions. See NARSTO (2002) for

30 further details regarding the calculation of emissions inventories.

31

TABLE 9-2. EMISSIONS OF PRIMARY PM$_{2.5}$ BY VARIOUS SOURCES IN 1999

Source	Emissions (10^9 kg/y)	Major PM Components	Notes
On-road vehicle exhaust	0.21	Organic compounds, elemental carbon	Exhaust emissions from diesel (72%) and gasoline vehicles (28%).
Non-road vehicle exhaust	0.37	Organic compounds, elemental carbon	Exhaust emissions from off-road diesel (57%) and gasoline vehicles (20%); ships and boats (10%); aircraft (7%); railroads (6%).
Fossil fuel combustion	0.36	Crustal elements, trace metals	Fuel burning in stationary sources such as power plants (33%); industries (39%); businesses and institutions (25%); residences (3%).
Industrial processes	0.35	Metals, crustal material, organic compounds	Metals processing (29%); mineral products (27%); chemical mfg. (11%); other industries (33%).
Biomass burning	1.2	Organic compounds, elemental carbon	Managed burning (47%); residential wood burning (28%); agricultural burning (7%); wildfires (18%).
Waste disposal	0.48	Organic compounds, trace metals	Open burning (91%); incineration (9%).
Fugitive dust	3.3	Crustal elements	Dust raised by vehicles on paved (19%) and unpaved roads (40%); construction (15%), dust from raising crops (24%) and livestock (2%).
Windblown dust	NA[1]	Crustal elements	Dust raised by wind on bare land.
Other	0.02	Organic compounds, elemental carbon	Structural fires
Total	6.2		

[1]NA = not available.

Source: Adapted from U. S. Environmental Protection Agency (2001).

1   Although most emphasis in this section has been placed on sources within the United

2 States, it also should be remembered that sources outside the United States contribute to ambient

3 PM levels that can, at times, exceed the ambient NAAQS. Dense hazes, composed mainly of

4 dust, occur frequently during the summer in southern Florida. This dust has been emitted in the

5 Sahara Desert and then transported across the Atlantic Ocean. Large-scale dust storms in the

6 deserts of central Asia recently have been found to contribute to PM levels in the Northwest on

7 an episodic basis. Not only dust but microbial pathogens and various pollutants are transported

TABLE 9-3. EMISSIONS OF PRECURSORS TO SECONDARY PM$_{2.5}$ FORMATION BY VARIOUS SOURCES IN 1999

Precursor	Emissions (10^9 kg/y)	Secondary PM Component	Notes
SO$_2$	17	Sulfate	Exhaust from on-road (2%) and non-road (5%) engines and vehicles; fossil fuel combustion by electrical utilities, industries, other sources (85%); various industrial processes (7%); and other minor sources (1%).
NO$_x$[1,2]	26	Nitrate	Exhaust from on-road (34%) and non-road (22%) engines and vehicles; fossil fuel combustion by electrical utilities, industries, other sources (39%); lightning (4%); soils (4%); and other minor sources (5%).
Anthropogenic VOCs	16	Various mainly unidentified compounds of 'OC'	Evaporative and exhaust emissions from on-road (29%) and non-road (18%) vehicles; evaporation of solvents and surface coatings (27%); biomass burning (9%); storage and transport of petroleum and volatile compounds (7%); chemical and petroleum industrial processes (5%); other sources (5%).
Biogenic VOCs[1]	44	Various mainly unidentified compounds of 'OC'	Approximately 98% emitted by vegetation. Isoprene (35%); monoterpenes (25%); all other reactive and non-reactive compounds (40%).
NH$_3$	45	Ammonium	Exhaust from on-road and non-road engines and vehicles (5%); chemical manufacturing (3%); waste disposal, recycling, and other minor sources (5%); livestock (82%); and fertilizer application (18%).

[1]Includes estimates of natural sources from Guenther et al. (2000).
[2]Emissions expressed in terms of NO$_2$.

Source: Adapted from U. S. Environmental Protection Agency (2001).

1   during these events. Uncontrolled biomass burning in central America and Mexico may have

2   contributed to elevated PM levels that exceeded the daily NAAQS level for PM in Texas; and

3   wildfires throughout the United States, Canada, Mexico, and Central America all contribute to

4   PM background concentrations in the United States.

5

6

9.4 AMBIENT CONCENTRATIONS

What are the basic characteristics of ambient monitoring data used to draw inferences about the relations between health outcomes and air pollution?

9.4.1 Measurement of Particulate Matter

It is possible to measure a variety of PM indicators with high precision. However, the absolute accuracy of a PM monitoring techniques cannot be established because no standard reference calibration material or procedure has been developed for suspended, atmospheric PM. Therefore, accuracy is defined as the degree of agreement between a field PM sampler and a collocated PM reference method audit sampler. Intercomparison studies, therefore, are very important for establishing the reliability of PM measurements.

One important measurement problem arises from the presence of semivolatile components (i.e., species that exist in the atmosphere in dynamic equilibrium between the condensed phase and gas phase) in atmospheric PM. Important examples include ammonium nitrate, semivolatile organic compounds, and particle-bound water. Most filter-weighing techniques for PM, including the U.S. Federal Reference Methods (FRM), require equilibration of collected material at fixed, near-room temperature (25 °C) and moderate relative humidity (40%) to reduce particle-bound water. This also causes the loss of an unknown, but possibly significant fraction, of ammonium nitrate and semivolatile organic compounds. Some modest amount of particle-bound water may be present at the 40 % relative humidity at which filter samples are equilibrated. However, to avoid measurement of large amounts of particle-bound water that would be present at higher relative humidities, continuous measurement techniques must reduce particle-bound water *in situ*. One technique is to stabilize PM at a specified temperature high enough to remove all, or almost all, particle-bound water. This results in loss of much of the semivolatile PM. Examples include the tapered element oscillating microbalance (TEOM) operated at 50 ºC and beta gauge monitors with heated inlets. Another technique is the use of a diffusion denuder to remove water vapor without heating. Examples include the Brigham Young absorptive sampler and Harvard pressure drop monitor. The three approaches give different mass concentrations, especially in air sheds with high nitrate, wood smoke, or secondary organic aerosols. Current PM standards are based on health effects studies mainly using filter techniques. However, the

1   need to provide new real time information to the public and the economic pressure to replace

2   filter samplers with continuous monitors will require a better understanding of the physics and

3   chemistry of the semivolatile components of PM and studies of the potential health effects of

4   these components.

5

6   ### 9.4.2 Mass Concentrations

7   Data for ambient $PM_{2.5}$ and PM_{10} concentrations are obtained routinely by networks

8   operated by various state and local agencies. Data are also collected as part of research efforts by

9   governmental, academic and industrial groups. Data from state and local agencies are stored in

10   the AIRS (Aerometric Information Retrieval System) data base, maintained by the U.S.

11   Environmental Protection Agency. Concentrations of $PM_{10-2.5}$ based on FRM PM_{10} and $PM_{2.5}$

12   monitors are estimated by taking the difference between these two measurements. The spatial

13   coverage and frequency of sampling depends on the resources of the agency carrying out the

14   monitoring. Thus, the amount of data collected in a given urban area varies across the United

15   States.

16   The median $PM_{2.5}$ concentration was 13 $\mu g/m^3$ in the United States on a county basis, for

17   1999 and 2000. The corresponding median $PM_{10-2.5}$ concentration was about 10 $\mu g/m^3$ for the

18   same period. However, there was a good deal of variability in the annual means in different

19   environments in the United States. The mean $PM_{2.5}$ concentration was below 7 $\mu g/m^3$ in 5% and

20   below 18 $\mu g/m^3$ in 95% of counties that met minimum AIRS data completeness criteria for

21   calculation of an annual mean concentration (at least 11 days data for each calendar quarter).

22   The mean $PM_{10-2.5}$ concentration was below 4 $\mu g/m^3$ in 5% and below 21 $\mu g/m^3$ in 95% of

23   counties meeting the criteria given above. Mean $PM_{2.5}$ and $PM_{10-2.5}$ concentrations reported by

24   the IMPROVE network were considerably lower than the lowest 5th percentile values reported by

25   state and local agencies.

26   An adequate characterization of the PM concentrations found in urban areas cannot be

27   obtained by considering only annual average concentrations for the whole urban area. There can

28   be considerable spatial and temporal variability in the concentration fields. Typically, annual

29   mean concentrations are within 5 $\mu g/m^3$ of each other in urban areas (MSAs). The spread in

30   values can be much greater if CMSAs are considered. Even within some MSAs, concentrations

31   measured at separate sites on individual days can differ by over 100 $\mu g/m^3$.

1   Pairs of sites within MSAs are correlated with each other to varying degrees, depending on

2   the urban area. There are some very general regional patterns evident in the data base in which

3   sites tend to be more highly correlated with each other in the eastern United States and less well

4   correlated with each other in the western United States. Figure 9-6 shows an example for

5   Philadelphia, PA. The exceptions are frequent enough to prevent extrapolation from one city to

6   another without first examining the data. Although sites may be highly correlated with each

7   other within an MSA, this does not mean that the concentration fields are uniform, as illustrated

8   by Figure 9-7 for three urban areas. Concentrations for the three site pairs chosen are all well

9   correlated with each other ($r>0.9$), but the concentrations display different degrees of uniformity.

10

9.4.3 Physical and Chemical Properties of Ambient PM

12   Physical and chemical properties of fine-mode and coarse-mode particles that are produced

13   by sources listed in Table 9-1 are summarized in Table 9-4. It can readily be seen that fine- and

14   coarse-mode particles show striking differences in the nature of their sources, their composition,

15   and hence, their chemical properties, and in their removal processes. Differences in sources and

16   removal processes for fine- and coarse-mode particles account for many differences in their

17   behavior in the atmosphere. The much shorter atmospheric lifetimes of coarse particles

18   compared to fine particles implies that fine particles can travel much further in the atmosphere

19   than coarse particles. The more sporadic nature of the sources of coarse particles, in addition,

20   implies that coarse PM should be more highly spatially variable than fine PM. Elemental

21   compositions, including trace elements by X-ray flourescence analysis, for $PM_{2.5}$ and $PM_{10-2.5}$ in

22   two cities with different fine/coarse relationships are given in Table 9-5. The major chemical

23   components of $PM_{2.5}$ from several sites in the eastern, interior, and western parts of the United

24   States are shown in Figure 9-8.

25

26

27

a.

	AIRS Site ID
Site A	34-007-0003
Site B	34-007-1007
Site C	42-045-0002
Site D	42-101-0004
Site E	42-101-0136

0   50   100 km

b.

AIRS ID#	3400700031	3400710071	4204500021	4210100041	4210101361
Mean	14.941	15.427	15.992	14.823	14.718
Obs	108	103	112	284	278
SD	8.524	8.749	8.265	8.537	8.295

c.

Site	A	B	C	D	E
A	1	0.964 (3.3, 0.082) 95	0.868 (6.3, 0.155) 98	0.88 (4.8, 0.129) 81	0.868 (5.4, 0.147) 80
B		1	0.849 (6.9, 0.158) 94	0.894 (3.7, 0.135) 77	0.857 (6.4, 0.148) 79
C			1	0.868 (5.0, 0.149) 85	0.818 (6.6, 0.154) 83
D				1	0.918 (4.9, 0.13) 246
E					1

Figure 9-6. Philadelphia, PA-NJ MSA. *(a)* **Locations of sampling sites by AIRS ID#;** *(b)* **Quarterly distribution of 24-h average PM$_{2.5}$ concentrations;** *(c)* **Intersite correlation statistics, for each data pair, the correlation coefficient, (P$_{90}$, coefficient of divergence) and number of measurements are given.**
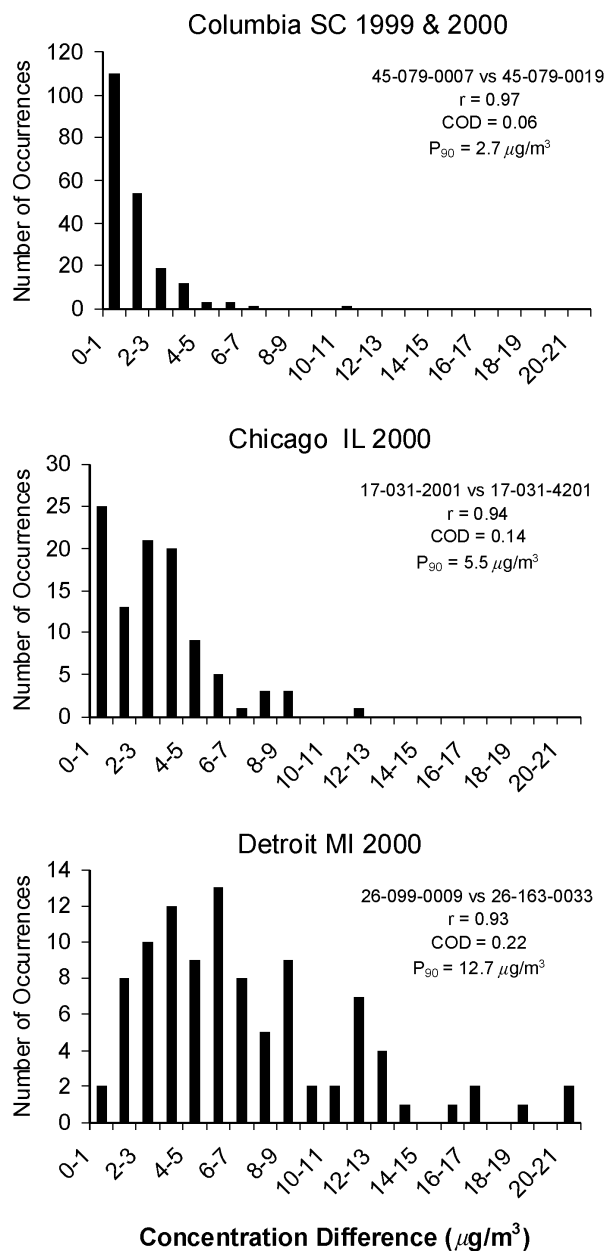
Figure 9-7. Occurrence of differences between pairs of sites in three MSAs. The absolute differences in daily average $PM_{2.5}$ concentrations between sites are shown on the x-axis and the number of occurrences on the y-axis. The MSA, years of observations, AIRS site I.D. numbers for the site pairs, Pearson correlation coefficients (r), coefficients of divergence (COD), and 90th percentile (P_{90}) difference in concentration between concurrent measurements are also shown.

Source: Pinto et al. (2002).

TABLE 9-4. COMPARISON OF AMBIENT PARTICLES, FINE MODE (Nuclei Mode Plus Accumulation Mode) AND COARSE MODE

	Fine		Coarse
	Nuclei	Accumulation	
Formation Processes:	Combustion, high-temperature processes, and atmospheric reactions		Break-up of large solids/droplets
Formed by:	Nucleation Condensation Coagulation	Condensation Coagulation Reactions of gases in or on particles Reactions of gases in or on particles Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding, abrasion of surfaces) Evaporation of sprays Suspension of dusts Reactions of gases in or on particles
Composition:	Sulfates Elemental Carbon Metal compounds Organic compounds with very low saturation vapor pressure at ambient temperature	Sulfate, Nitrate, Ammonium, and Hydrogen ions Elemental carbon Large variety of organic compounds Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc. Particle-bound water	Suspended soil or street dust Fly ash from uncontrolled combustion of coal, oil, and wood Nitrates/chlorides from HNO_3/HCl Oxides of crustal elements (Si, Al, Ti, Fe) $CaCO_3$, NaCl, sea salt Pollen, mold, fungal spores Plant and animal fragments Tire, brake pad, and road wear debris
Solubility:	Probably less soluble than accumulation mode	Largely soluble, hygroscopic, and deliquescent	Largely insoluble and nonhygroscopic
Atmospheric half-life:	Minutes to hours	Days to weeks	Minutes to hours
Removal Processes:	Grows into accumulation mode	Forms cloud droplets and rains out Dry deposition	Dry deposition by fallout Scavenging by falling rain drops
Travel distance:	<1 to 10s of km	100s to 1000s of km	<1 to 10s of km (100s to 1000s in dust storms)

Source: Adapted from Wilson and Suh (1997).

TABLE 9-5. CONCENTRATIONS OF PM$_{2.5}$, PM$_{10-2.5}$, AND SELECTED ELEMENTS IN THE PM$_{2.5}$ AND PM$_{10-2.5}$ SIZE RANGE

| | Phoenix, AZ (n = 164) | | | Philadelphia, PA (n = 20) | |
| | Concentration (ng/m^3) | | | Concentration (ng/m^3) | |
Species	PM$_{2.5}$	PM$_{10-2.5}$	Species	PM$_{2.5}$	PM$_{10-2.5}$
Mass	11,200	27,600	Mass	29,800	8,400
Al	125	1879	Al	109	325
Si	330	535	Si	191	933
P	11	37	P	15	28
S	487	131	S	3,190	38
Cl	19	208	Cl	23	47
K	110	561	K	68	100
Ca	129	1,407	Ca	63	421
Ti	11	130	Ti	8.7	30
V	0.7	2.0	V	9.7	3.2
Cr	0.6	2.6	Cr	1.4	1.0
Mn	5.7	29	Mn	3.2	6.3
Fe	177	1,211	Fe	134	352
Co	−0.4	1.2	Co	0.8	−0.2
Ni	0.6	1.8	Ni	8.5	2.0
Cu	5.2	10.3	Cu	7.7	14
Zn	17	25	Zn	56	52
As	1.9	0.6	As	0.4	0
Se	0.4	−0.02	Se	1.3	−0.1
Br	3.8	0.8	Br	14	3.0
Pb	6.6	4.6	Pb	28	13

Source: Zweidinger et al. (1998); Pinto et al. (1995).
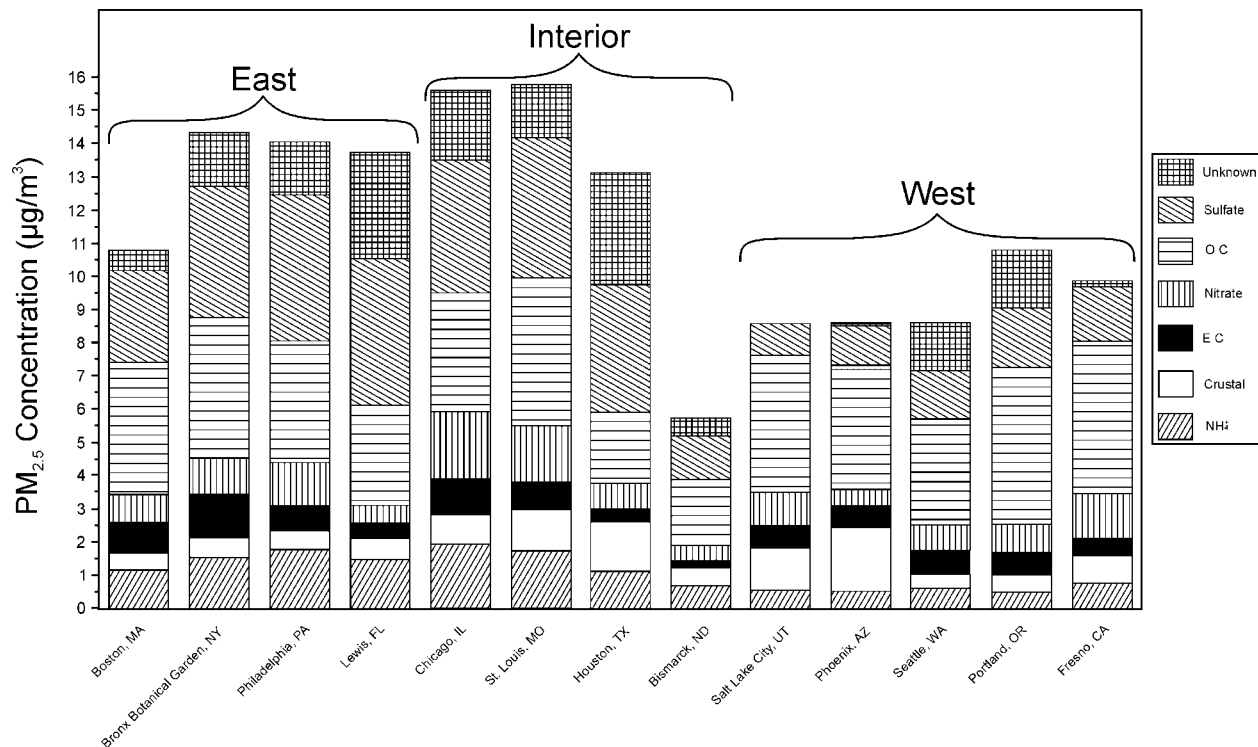
Figure 9-8. **Major chemical components of PM$_{2.5}$ as determined in the pilot study for EPA's national speciation network.**

9.5 AIR QUALITY MODEL DEVELOPMENT AND TESTING

2   *What are the linkages between emissions sources and the biologically important*

3   *components of particulate matter?*

4

5   Atmospheric models that address this question fit into two general categories. Either they

6   are process oriented and attempt to predict variables of interest based on the solution of equations

7   describing basic physical and chemical processes or they are statistically oriented and rely on the

8   statistical analysis of atmospheric data to infer information about the nature and relative

9   importance of different sources. Although there are many sub-categories within each of these

10   two broad categories, the two main types of models that are under active development and

11   application are chemistry-transport models (CTMs) and receptor models.

12

1   The main components of a CTM are summarized in Figure 9-9. Models such as the

2   CMAQ (Community Model for Air Quality) system and MAQSIP (Multiscale Air Quality

3   Simulation Platform) incorporate the processes shown in Figure 9-9 as numerical algorithms to

4   predict time dependent concentration fields of a wide variety of gaseous and particulate phase

5   pollutants. Also shown in Figure 9-9 is the meteorological model used to provide the inputs for

6   calculating the transport of species in the CTM. The meteorological models such as the MM5

7   model, which supples these inputs to the CTMs mentioned above, also provide daily weather

8   forecasts. The domains of these models extend typically over several thousand kilometers by

9   several thousand kilometers. Because these models are computationally intensive, it is often

10   impractical to run them over larger domains without sacrificing some features. For these

11   reasons, both the meteorological model and the CTM must have boundary conditions that allow

12   the effects of processes occurring outside the model domain to be felt. The entire system of

13   meteorological model emissions processors and output processors constituents the framework of

14   EPA's Models-3.

15
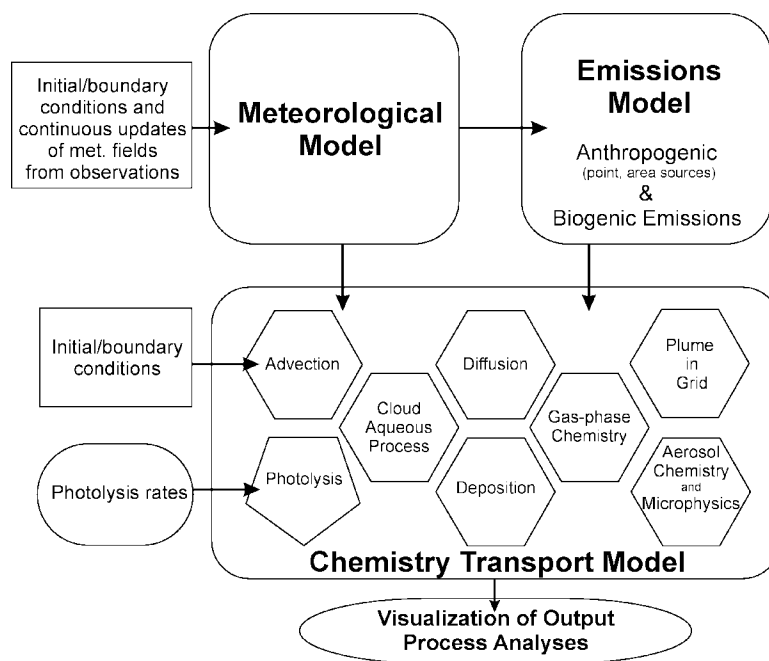
Figure 9-9.   Main components of a comprehensive atmospheric chemistry modeling system, such as Models 3.

1   The performance of models such as these must be evaluated by comparison with field data

2   as part of a cycle of model improvements and subsequent evaluations. Discrepancies between

3   model predictions and observations can be used to point out gaps in current understanding of

4   atmospheric chemistry. Very often, however, the algorithms in the model are 'tuned' to improve

5   agreement between the model predictions and a particular set of observations. Model evaluation

6   does not merely involve a straightforward comparison between model predictions and the

7   concentration field of the pollutant of interest. Even this task is not straightforward in the case of

8   PM, because PM is composed of a number of different substances with different chemical and

9   physical properties. A comparison of model predicted $PM_{2.5}$ mass with measured $PM_{2.5}$ mass

10   may not be very meaningful because there can be compensating errors in the model calculations

11   and there are significant artifacts affecting the collection and retention of a number of PM

12   components such as semi-volatile organic compounds and ammonium nitrate. Because of the

13   number and complexity of the parameterizations used in CTMs, there may be compensating

14   errors and tests of these parameterizations must be made for individual physical and chemical

15   processes.

16   Another issue relates to the averaging time that is used for both the observations and the

17   model outputs. Model predictions can be made with time steps shorter than an hour, however, as

18   noted in Chapters 2 and 3, there is a considerable degree of uncertainty associated with individual

19   hourly observations by continuous monitors. Emissions inventories, as shown in Tables 9-2 and

20   9-3, represent annual averages; and it is impractical, except in a few cases, to increase that

21   resolution down to even a few days. At least for modeling ozone, it has been found that

22   agreement between model and observations is improved if seasonal averages, rather than

23   episodic averages are considered.

24   Models such as the CTMs discussed above have been under development for a number of

25   years. Discussions of these models have not been included in the earlier chapters because these

26   models are not yet being used to provide information about human exposures that could be

27   incorporated into this document. CTMs are being used to develop emissions control strategies

28   and to aid in implementation of existing air quality standards. The reader is referred to NARSTO

29   documents (NARSTO, 2002) for further details.

30   There are two main approaches to receptor modeling. Receptor models such as the

31   chemical mass balance (CMB) model relate source category contributions to ambient

1   concentrations based on analyses of the composition of ambient PM and source emissions

2   samples. This technique has been developed for apportioning source categories of primary PM

3   and was not formulated to include the processes of secondary PM formation. In the second

4   approach, various forms of factor analysis are used. They rely on the analysis of time series of

5   compositional data from ambient samples to derive both the composition of sources and the

6   source contributions. Standard approaches such as factor analysis or Principal Component

7   Analysis (PCA) can apportion only the variance and not the mass in an aerosol composition data

8   set. Positive matrix factorization (PMF) is a recently developed multivariate technique that

9   overcomes many of the limitations of standard techniques, such as principal components analysis

10   (PCA), by allowing for the treatment of missing data and data near or below detection limits.

11   This is accomplished by weighting elements inversely according to their uncertainties. Standard

12   methods such as PCA weight elements equally regardless of their uncertainty. Solutions also are

13   constrained to yield nonnegative factors. Both the CMB and the PMF approaches find a solution

14   based on least squares fitting and minimize an object function. Both methods provide error

15   estimates for the solutions based on estimates of the errors in the input parameters. It should be

16   remembered that the error estimates often contain subjective judgments. For a complete

17   apportionment of mass, all of the major sources affecting a monitoring site must be sampled for

18   analysis by CMB, whereas there is no such restriction in the use of PMF.

19   Among other approaches, the UNMIX model takes a geometric approach that exploits the

20   covariance of the ambient data to determine the number of sources, the composition and

21   contributions of the sources, and the uncertainties (Henry, 1997). A simple example may help

22   illustrate the approach taken by UNMIX. For example, in a two-element scatter plot of ambient

23   Al and Si, a straight line and a high correlation for Al versus Si can indicate a single source for

24   both species (soil), while the slope of the line gives information on the composition of the soil

25   source. In the same data set, iron may not plot on a straight line against Si, indicating other

26   sources of Fe in addition to soil. More importantly, the Fe-Si scatter plot may reveal a lower

27   edge. The points defining this edge represent ambient samples collected on days when the only

28   significant source of Fe was soil. Success of the UNMIX model hinges on the ability to find

29   these "edges" in the ambient data from which the number of sources and the source compositions

30   are extracted. UNMIX uses principal component analysis to find edges in m-dimensional space,

31   where m is the number of ambient species. UNMIX does not make explicit use of errors or

1 uncertainties in the ambient concentrations, unlike the methods outlined above. This is not to

2 imply that the UNMIX approach regards data uncertainty as unimportant, but rather that the

3 UNMIX model results implicitly incorporate error in the ambient data. The underlying

4 philosophy here is that the uncertainties are often unquantifiable, and hence it is best to make no

5 a priori assumptions about what they are.

6 　　　For most practical purposes, the relative contributions of sources to ambient PM samples

7 are determined by receptor models. Receptor models have most successfully been applied to the

8 determination of sources of primary PM. The process based models are more flexible and could

9 be used for determining sources of secondary PM. However, they are computationally much

10 more intensive, and they rely on a large number of inputs, with varying degrees of uncertainty.

11 Arguably, emissions inventories represent the major source of uncertainty in the application of

12 CTMs (see e.g., Calvert et al., 1993). However, significant uncertainty also exists in

13 photochemical transformations, in part because of a lack of data for many key reactions. Further

14 uncertainty is added in the methods that are used to reduce the literally thousands of reactions

15 involving hundreds of species occurring in the atmosphere to more tractable numbers through the

16 use of idealized chemical mechanisms. Issues concerning the gas phase mechanisms are relevant

17 because the free radicals that are involved in the formation of photochemical oxidants are also

18 involved in the formation of secondary PM.

19

20

21 ## 9.6 EXPOSURE TO PARTICULATE MATTER AND COPOLLUTANTS

22 　　　*What are the quantitative relationships between concentrations of particulate matter and*

23 *gaseous copollutants measured at stationary outdoor air-monitoring sites and the contributions*

24 *of these concentrations to actual personal exposures, especially for subpopulations and*

25 *individuals?*

26

27 　　　It will be useful to separate these relationships into two components: (a) central site to

28 outdoor concentrations; and (b) outdoor concentrations to personal exposures.

29

30

31

9.6.1 Central Site to Outdoor

The first component to be examined is the relationship between ambient PM concentrations measured by a central monitor, located at a site presumably representative of the community (or the average of several such sites), and the ambient PM concentration just outside an indoor microenvironment such as a home.

9.6.1.1 Exposure for Acute Epidemiology

In acute time-series studies, daily deaths (or other health effects) are regressed against the daily ambient PM concentrations as measured at a single site (or the average of several sites) in a city. Spatial variations in daily exposure can lead to errors in the estimated relative risk. Under the assumption of a linear relationship between exposure and effect, analysis of exposure error suggests that a key indicator of the effect on epidemiologic results of spatial variations in exposure will be the strength of the daily site-to-site **correlations** of ambient PM concentrations. Chapter 3 presents a substantial body of new monitoring data from AIRS. A range of correlations of $PM_{2.5}$ concentrations were found between monitoring sites in the cities chosen for analysis. PM_{10} and TSP sites were frequently chosen to monitor specific local point or area sources. However, $PM_{2.5}$ sites are chosen primarily to be representative of community exposures. Still it would be wise to check the representativeness of a site before choosing a site or group of sites to provide a representative community concentration for exposure or epidemiologic studies. As shown in Figure 9-10, site-to-site correlations tend to be higher for a site pair where both of which are dominated by regional PM than for a site pair where one of which is more strongly influenced by local sources.

9.6.1.2 Exposure for Chronic Epidemiology

In chronic studies, total or annual deaths in large cohorts in different cities are regressed against long-term or annual average concentrations in the different cities. Few analyses of exposure error have been performed for this case. However, the key consideration for chronic studies might be differences in the annual (or seasonal) **averages** in different parts of a city. Prior to NRC-1, there was little information on the variations of long term PM concentration averages across cities. Some information on the spatial variations in long-term (seasonal) averages are reported in Chapter 3 of this document, based on data from AIRS.
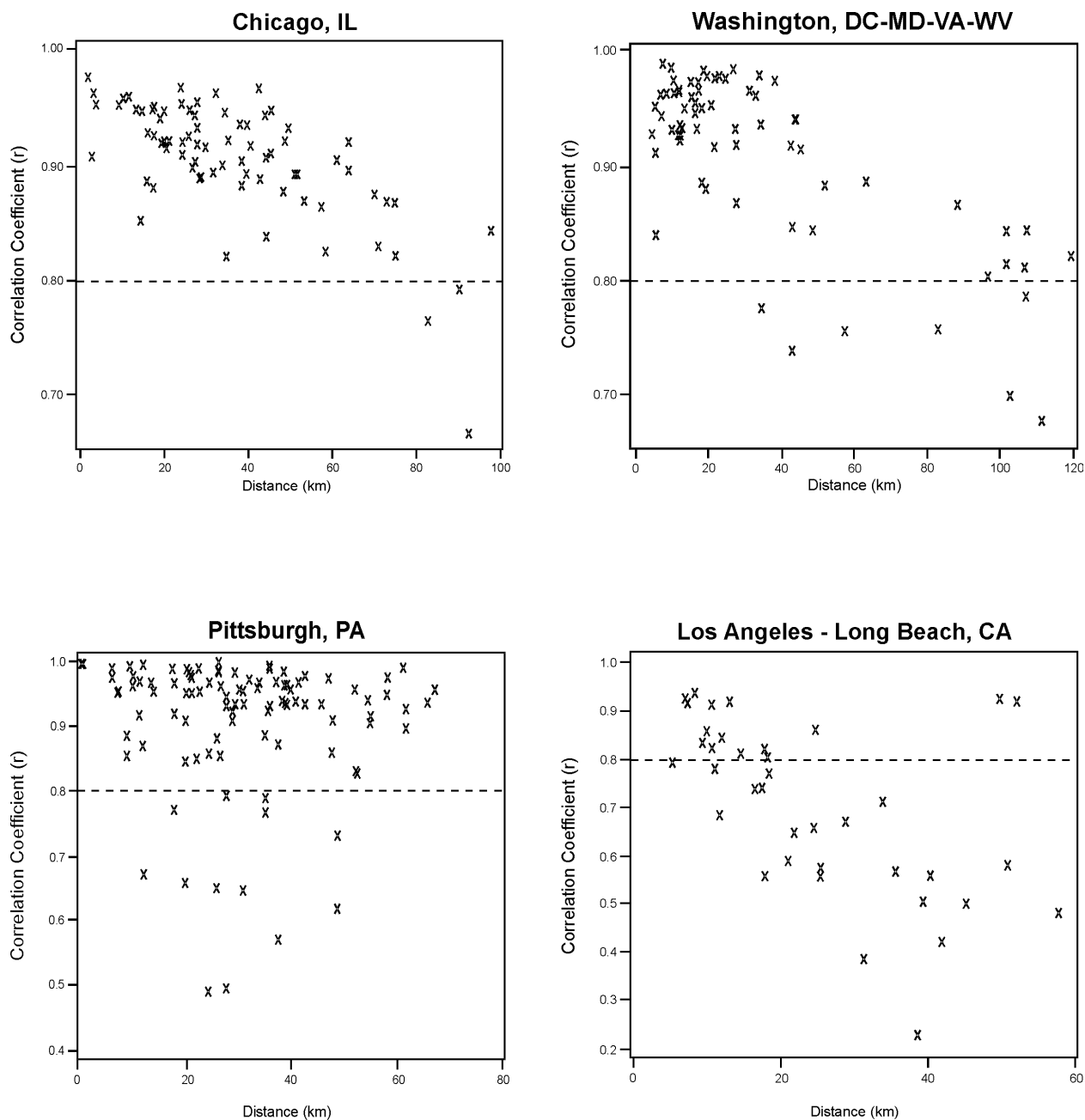
Figure 9-10. Correlograms showing the variation in site-to-site correlation coefficient for PM$_{2.5}$ as a function of distance between sites for several cities.

Source: Fitz-Simons et al. (2000).

9.6.2 Home Outdoor Concentrations Versus Ambient Concentrations Indoors and the Ambient Contribution to Total Personal Exposure

What is the relationship between the concentration of ambient PM outside a home and the concentration of ambient PM that has infiltrated into the home?

9.6.2.1 Mass Balance Model

It will be useful to review some concepts derived from the equilibrium mass balance model, discussed in detail in Chapter 5. The ratio of the ambient PM concentration outdoors, C, to the concentration of ambient PM that has infiltrated indoors, $C(AI)$, is given by the infiltration factor where P is the particle penetration efficiency, a is the air exchange rate, and k is the deposition rate.

$$C(AI)/C = Pa/(a+k) = F_{INF} \text{ (the infiltration factor)} \qquad (9\text{-}1)$$

As will be discussed later, P and k are functions of the particle size, so F_{INF} will also depend on particle size. The mass balance equation may be modified to include particle removal by air handling systems and to account for nonequilibrium behavior.

While indoors, a person will be exposed to a concentration of ambient pollution given by $C \bullet F_{INF}$. However, while outdoors a person will be exposed to the full ambient concentration. The infiltration factor and the fraction of time outdoors may be used with the ambient concentration to estimate the ratio of the ambient PM exposure (while indoors and outdoors) to the ambient PM concentration, where y = the fraction of time spent outdoors,

$$A/C = y + (1\text{-}y)F_{INF} = y + (1\text{-}y)Pa/(a+k) = \alpha \text{ (the attenuation factor).} \qquad (9\text{-}2)$$

Since y and a may vary from day to day and person to person and P and k will vary with particle size, α will also be a variable.

It is necessary to understand the infiltration factor, used to estimate the concentration of ambient PM concentration indoors $[C(AI) = C \bullet F_{INF}]$, and the attenuation factor, used to estimate the ambient exposure, i.e., personal exposure to particles of ambient original, $[A = C \bullet \alpha]$,

1   because they may be estimated from exposure measurements and used to estimate A, the ambient

2   component of total personal exposure.

3

4   **9.6.2.2 Separation of Total Personal Exposure into its Ambient and Nonambient**
5   **Components**

6   A person's total exposure to PM or other pollutants includes a nonambient component,

7   usually divided into a component due to indoor-generated pollutants that are evenly distributed

8   through out the house and a component, sometimes called the personal cloud, due to activities of

9   the person that generate pollutants which influence that person more than other persons in the

10   same house. Thus, total personal exposure, T, equals the sum of ambient exposure, A, and

11   nonambient exposure, N:

12

13                                    $$T = A + N$$ (9-3)

14

15   As NRC Topic 1 makes clear, a key variable of interest is A, the ambient exposure, i.e., the

16   contributions of particulate matter and gaseous copollutants *measured at stationary outdoor*

17   *air-monitoring sites* to actual personal exposures, not T, the total personal exposures due to

18   ambient and indoor-generated pollutants. However, it is not possible to measure A or N directly.

19   Only T and C can be measured directly. It is necessary to understand the infiltration factor, used

20   to estimate the concentration of ambient PM concentration indoors, $[C(AI) = C \cdot F_{INF}]$, and the

21   attenuation factor, used to estimate the ambient exposure, $[A = C \cdot \alpha]$, because these factors may

22   be estimated from exposure measurements and used to estimate A, the ambient component of

23   total personal exposure.

24   In recent years, the need to separate personal exposure into ambient and nonambient

25   components has been recognized (Wilson and Suh, 1997), techniques for separating total

26   personal exposure into its ambient and nonambient components have been recommended

27   (Wilson et al., 2000), several papers have reported average values of α and N, and one paper has

28   reported individual values of A.

29

30   **Average Values**

31   As shown in Figure 9-11, regression of individual measurements of personal exposure on

32   the corresponding measurements of ambient concentrations yields two components of total
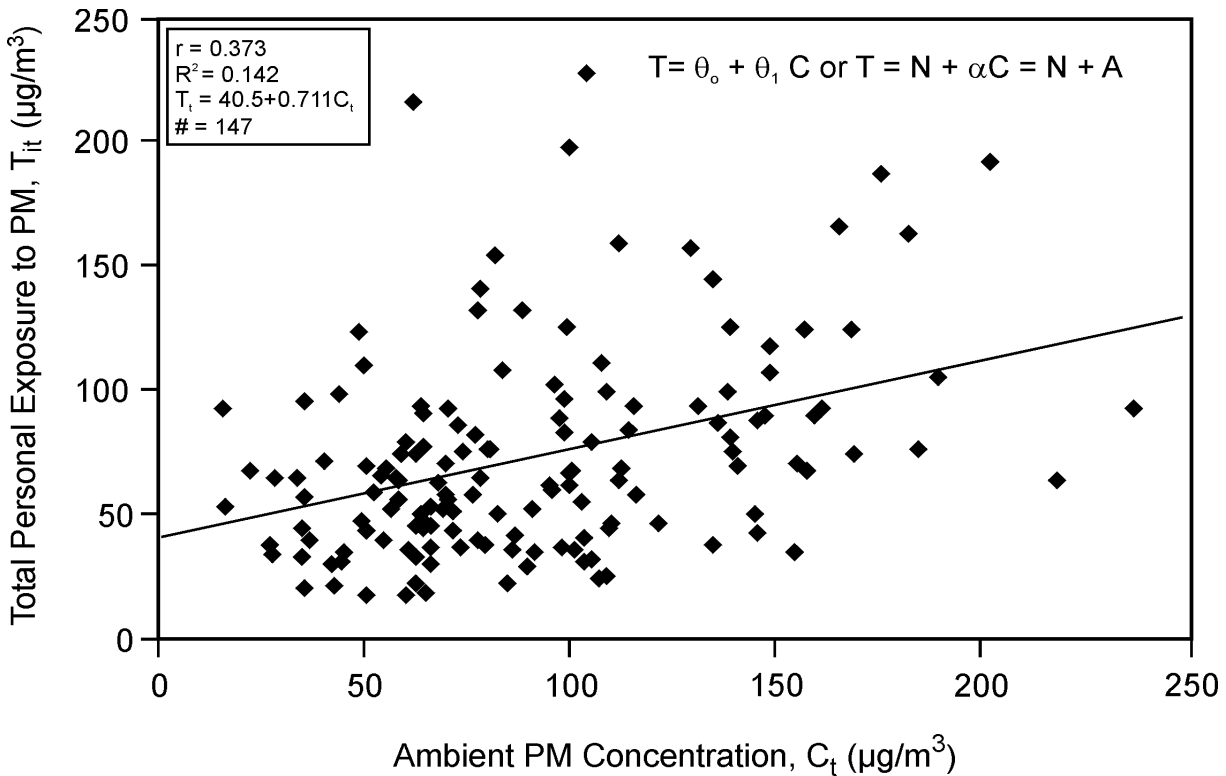
Figure 9-11. **Regression analysis of daytime total personal exposures to PM$_{10}$ versus ambient PM$_{10}$ concentrations using data from the PTEAM study. The slope of the regression line is interpreted by exposure analysts as the average α, where α$C = A$.**

Source: Wilson et al. (2000)

1   exposure, one dependent on concentration, one not ($T = \theta_0 + \theta_1 C$; Zeger et al., 2000). Exposure

2   analysts associate the component independent of concentration, θ_0 , with cohort average

3   nonambient exposure and the component dependent on concentration, θ_1, with alpha, α, the ratio

4   of ambient exposure to ambient concentration ($T = N + \alpha C = N + A$; Dockery and Spengler,

5   1981; Ott et al., 2000; Wilson et al., 2000). Most exposure studies report the correlation between

6   ambient concentrations and personal exposure, and many of these also report the slope of the

7   relationship. Since the slope may be interpreted as the average alpha there are a number of

8   studies from which estimates of the average alpha may be estimated. However, the slope may

9   not accurately reflect the average alpha unless the data has been examined for outliers. Several

1   studies have interpreted the slope and reported the average F_{INF} or α for cohorts (Ott et al., 2000;

2   Wilson et al., 2000; Patterson and Eatough, 2000; Landis et al., 2001).

3

4   **Individual Values**

5   The high correlations found between ambient sulfate and personal sulfate (which has few

6   indoor sources) suggest that a better relationship may be found between ambient concentrations

7   and ambient exposures than between ambient concentrations and total personal exposures to PM

8   (Figure 9-12). The PTEAM study provided sufficient information to permit estimation of

9   individual values of ambient PM_{10} exposure, A. These individual values of A were found to be

10   highly correlated with the corresponding ambient PM_{10} concentration, C (Figure 9-13) (Wilson

11   et al., 2000). It is also important to determine whether or not the nonambient exposure, N, is a

12   function of C, since if N is not correlated with C, N cannot be a confounder in a regression of

13   health effects on ambient concentration (Figure 9-14) (Zeger et al., 2000).

14

15
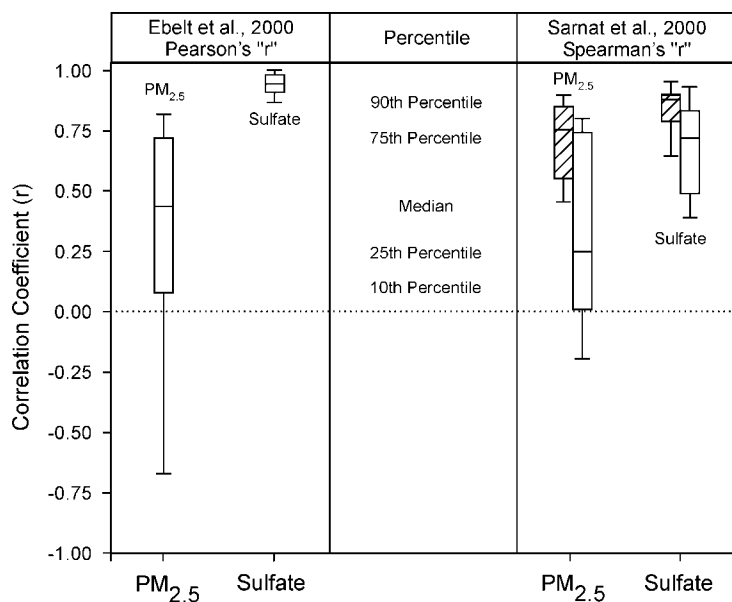
Figure 9-12.   Comparison of correlation coefficients for longitudinal analyses of personal exposure for individual subjects versus ambient concentrations of $PM_{2.5}$ and sulfate.

Source: Ebelt et al. (2000), Sarnat et al. (2000).
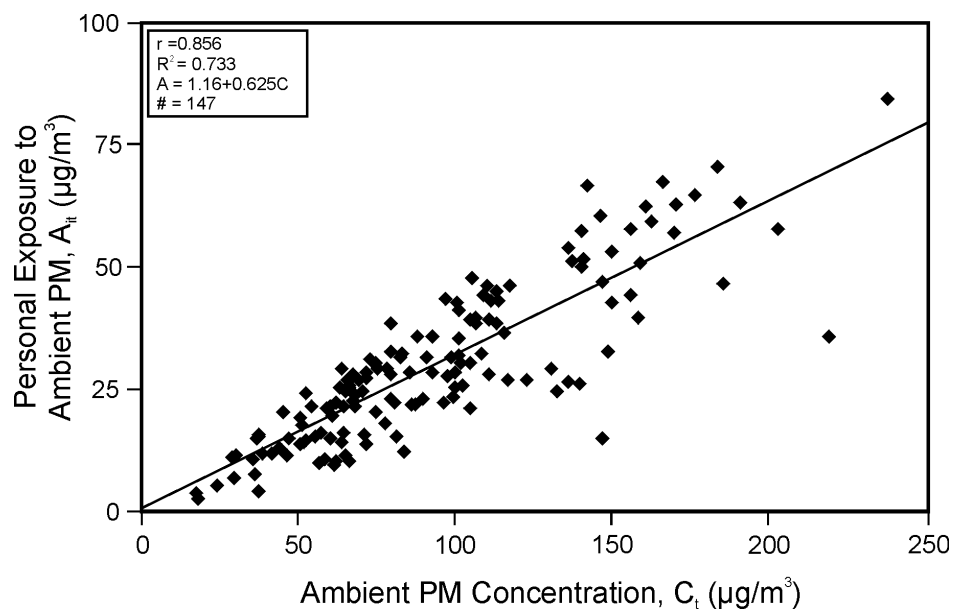
Figure 9-13. **Regression analysis of daytime exposures to the ambient component of personal exposure to PM_{10} (ambient exposure) versus ambient PM_{10} concentrations.**

Source: Wilson et al. (2000).
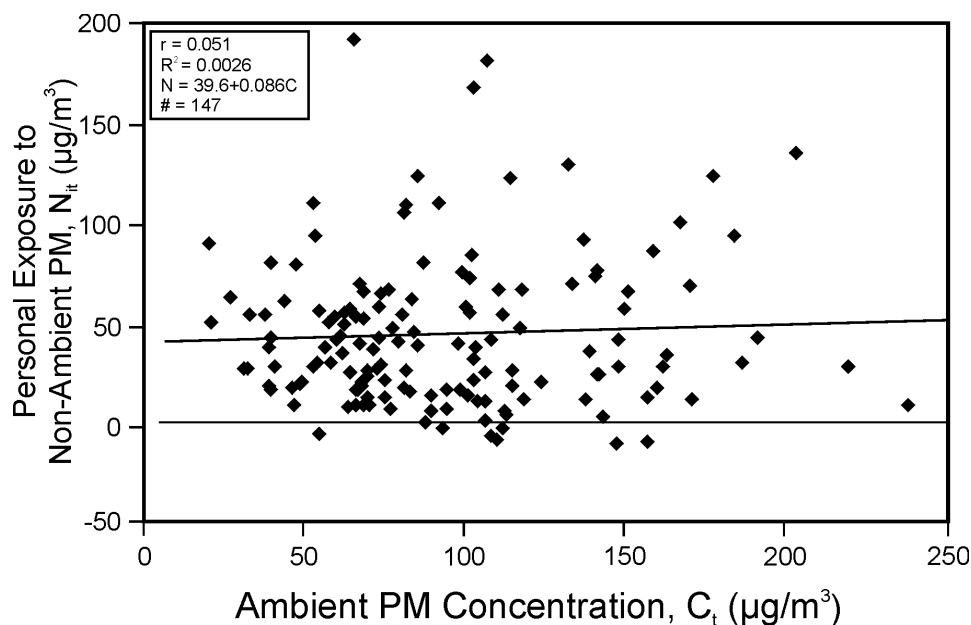
Figure 9-14. **Regression analysis of daytime exposures to the nonambient component of personal exposure to PM_{10} (nonambient exposure) versus ambient PM_{10} concentrations. The two variables are unrelated.**

Source: Mage et al. (1999)

9.6.3 Variability in the Relationship Between Concentrations and Personal Exposures

The values of the infiltration factor and alpha may vary from person-to-person as shown by the distribution of the infiltration factor and alpha in the PTEAM study (Figure 9-15) (Wilson et al., 2000). The average value of alpha may vary from season-to-season and from city-to-city. The variation in average alpha across cities, as estimated by city-to-city air-conditioning use, can explain some of the variation in the quantitative effects of particles on health across cities (Figure 9-16) (Janssen et al., 2002). For a given PM component, the air exchange rate, a, is a major factor in determining the relationship between outdoor and personal exposure. This has been shown in a study in which personal exposure data were classified into three groups based on home ventilation status. High values of alpha and high correlations were found for the well-ventilated homes, lower values for moderately well-ventilated homes, and much lower values for poorly ventilated homes.

9.6.4 Exposure Relations for Co-Pollutants

The key issue is whether the gaseous co-pollutants (CO, NO_2, SO_2, and O_3) contribute to the health effects attributed to PM or whether they merely serve as surrogates for PM. If the gaseous co-pollutants were responsible for some or all of the health effects attributed to PM in a single pollutant, community time-series epidemiologic analysis, they would be contributors, and the health effects due to PM would be overestimated. However, if the gaseous co-pollutants were surrogates for PM, i.e., significantly correlated with PM but not contributing to the health effects attributed to PM in the analysis, in a multiple regression, the surrogate would share some of the health effect with the causal agent, especially if the surrogate were measured more accurately than the causal agent. Thus, use of a surrogate in a multiple regression would result in an underestimation of the health effects due to PM.

In community, time-series epidemiology, in which daily, community-average health effects are regressed against daily ambient concentrations, there are several requirements that must be met in order for a gaseous co-pollutant to be a contributor to the health effects attributed to PM. (1) The gaseous co-pollutant must be capable of causing the effect at the level of the community exposure, (2) the daily ambient concentrations of the gaseous co-pollutant must be related to (i.e., correlated with) the daily ambient concentrations of the PM indicator, and (3) the daily ambient

Fraction of Ambient PM$_{10}$ Found Indoors (F$_{INF}$ = C(AI)/C)

Fraction of Ambient PM$_{10}$ Found in Personal Exposure (α =A/C)
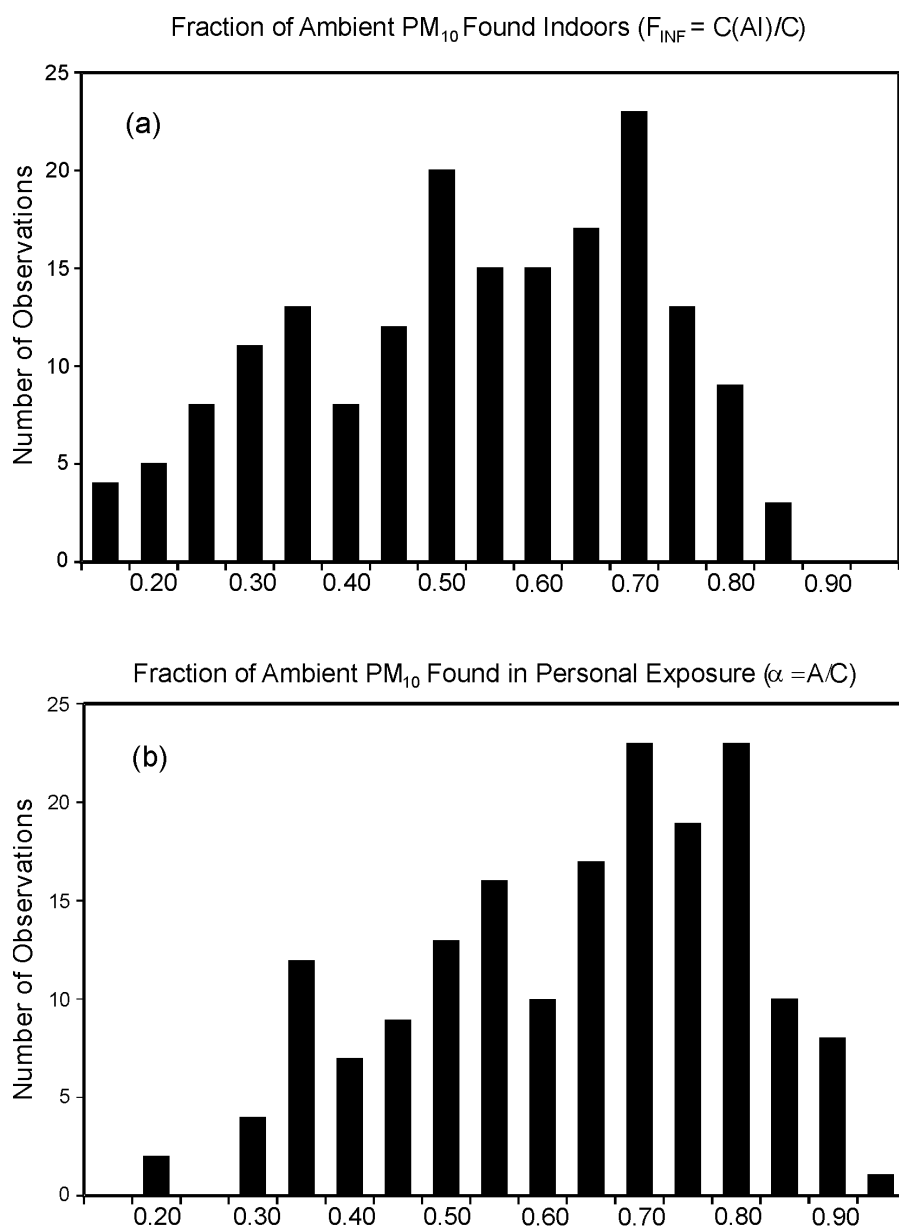
Figure 9-15. **Distribution of individual, daily values of the infiltration factor, F_{INF} = C(AI)/C and the attenuation factor, α = A/C, estimated using data from the PTEAM study. The distribution of the attenuation factor is shifted to higher values compared to the infiltration factor because people are exposed to the full ambient concentration when outdoors.**

Source: Wilson et al. (2000).
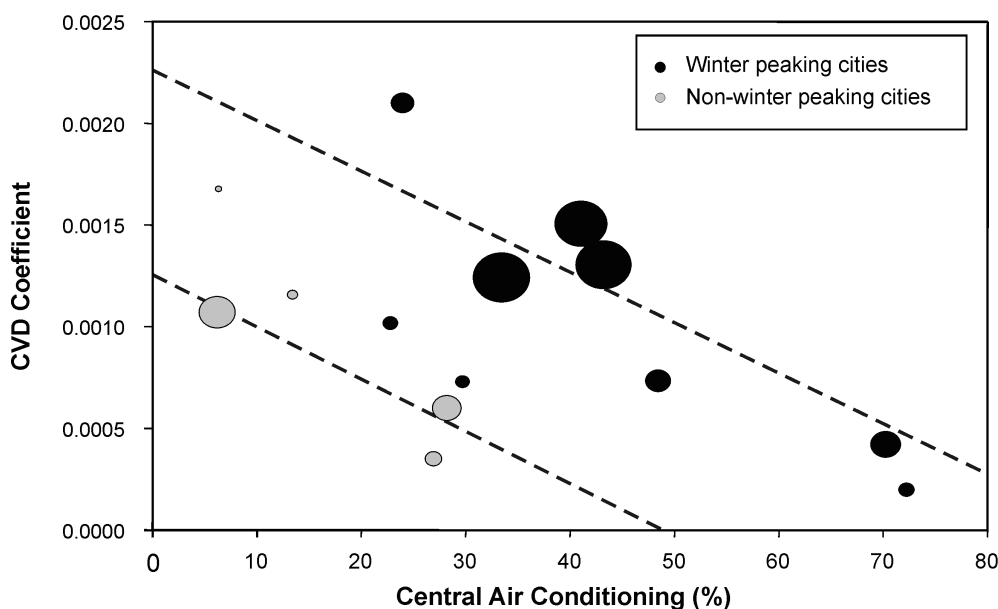
Figure 9-16. **Percentage of homes with air conditioning versus the regression coefficient for the relationship of cardiovascular-related hospital emissions to ambient PM_{10} concentrations. The higher the percent air conditioning, the lower the amount of personal exposure to ambient PM per unit of ambient PM concentration, i.e., lower α, and there a lower regression coefficient (increase in risk per until PM_{10} exposure).**

Source: Janssen et al. (2002).

1   concentrations of the gaseous co-pollutant must be related to (correlated with) the personal

2   exposures to that gaseous co-pollutant. Requirements 1 and 2 are also requirements for being a

3   "confounder" in epidemiologic and biostatistics terminology. Whether or not requirement 3 is

4   also a requirement for confounding will depend on the exact definition used for confounding.

5   A fourth requirement, that may apply to confounding, is that the gaseous co-pollutant not be in

6   the formation pathway of the PM. Since SO_2 and NO_2 are in the formation pathway for the

7   sulfate and nitrate components of PM and O_3 is a key chemical reactant in the formation of the

8   sulfate, nitrate, and organic components of PM, this fourth requirement has implications for

9   possible confounding of PM by gaseous co-pollutants that have not yet been adequately analyzed.

10   The exposure analyst is concerned with requirements 2 and 3. How well are the daily

11   ambient concentrations of the gaseous co-pollutants correlated with the daily ambient

1 concentrations of PM (or specific PM components or indicators) and are the daily ambient

2 concentrations of the gaseous co-pollutants correlated with the daily personal exposures to the

3 ambient? In order to answer these questions quantitatively, information would be needed on the

4 spatial variability of PM indicators and the gaseous co-pollutants and on the variability of the

5 factors which control the infiltration factors (penetration factor and deposition or removal rates).

6 　　　　Exposure relationships for gaseous co-pollutants were not reviewed in the exposure chapter

7 (Chapter 5) of this document. Although there have been many exposure studies of the gaseous

8 co-pollutants, there has been little analysis of the experimental data in terms relevant to

9 epidemiology. Exposure studies for CO, NO_2, and O_3 have been reviewed in the respective Air

10 Quality Criteria Documents (U.S. Environmental Protection Agency, 1993, 1996b, 2000a) and

11 exposure studies of the gaseous co-pollutants and PM components have been reviewed by Monn

12 (2001). Qualitative information on exposure relationships which may be inferred from the

13 studies reviewed in these publications are given in Table 9-6.

14

15

TABLE 9-6. QUALITATIVE ESTIMATES OF EXPOSURE VARIABLES

	Spatial Homogeneity[1]	Infiltration Factor[2]	Stability of the Infiltration Factor[3]
Highest	$SO_4^=$	CO	CO
High	$PM_{2.5}$	$PM_{2.5}$, $SO_4^=$, EC[4]	$PM_{2.5}$, $SO_4^=$, EC[4]
Medium	NO_2, O_3, $PM_{10-2.5}$, SO_2	NO_2	NO_2, $PM_{10-2.5}$, UF[5]
Low	CO, EC[4]	$PM_{10-2.5}$	O_3, SO_2
Lowest	UF[5]	UF[5], O_3, SO_2	

1. As indicated by the inverse size of the site-to-site correlation coefficient.
2. As indicated by the value of the infiltration factor, inferred in the case of gaseous co-pollutants from indoor/outdoor ratios for homes without known indoor sources.
3. As indicated by the inverse sensitivity of the deposition or removal rate to the surface to volume ratio and the chemical composition of the surface.
4. Elemental carbon.
5. Ultrafine particles.

1   Based on the estimates in Table 9-6, it might be expected that the correlation between daily

2   ambient concentrations of $PM_{2.5}$ and sulfate and personal exposure to $PM_{2.5}$ and sulfate would be

3   high and statistically significant but that this relationship would not be as significant for the

4   gaseous co-pollutants. Two recent studies (Sarnat et al., 2000, 2001) provide new information

5   relevant to the possible contribution of gaseous co-pollutants to the health effects attributed to

6   PM. Personal exposure measurements were made of NO_2, O_3, and sulfate (winter and summer)

7   and of SO_2 and EC (winter only). Ambient measurements were made of these species (same

8   seasons) and of CO (both seasons). Personal exposures to ambient $PM_{2.5}$ were estimated by

9   using the daily, individual ratios of personal exposure to sulfate to ambient concentrations of

10   sulfate as an estimate of the attenuation factor for $PM_{2.5}$. Correlations among ambient

11   concentrations, among personal exposures, and between ambient concentrations and personal

12   exposures were examined.

13   Daily personal exposures to NO_2 and O_3 were not significantly correlated with daily

14   ambient concentrations of those gaseous co-pollutants in either summer or winter. This suggests

15   that NO_2 and O_3 cannot be contributors to the health effects attributed to PM in an epidemiologic

16   analysis using daily ambient concentrations. In the winter, daily personal exposures to SO_2 were

17   negatively correlated with daily ambient concentrations of SO_2. Personal exposures to CO were

18   not reported. During summer, O_3 and NO_2 were positively and significantly associated with

19   $PM_{2.5}$; the association with CO was positive but not significant. During winter, CO and NO_2

20   were positively and significantly associated with $PM_{2.5}$ while O_3 was negatively and significantly

21   associated with $PM_{2.5}$; the association with SO_2 was negative but not significant. Similar

22   association of gaseous co-pollutants were found with personal exposure to $PM_{2.5}$ except that the

23   winter association with SO_2 became significant. Also, the significant associations were more

24   significant with personal exposure to ambient $PM_{2.5}$. This indicates that daily ambient

25   concentrations of CO, NO_2, O_3 and SO_2 can be surrogates for daily ambient concentrations of

26   $PM_{2.5}$ but that exposure and epidemiologic analyses including O_3 and SO_2 need to examine

27   relationships on a seasonal basis. These studies also indicate that daily ambient concentrations of

28   $PM_{2.5}$, CO, NO_2, O_3 and SO_2 serve as surrogates for daily personal exposures to $PM_{2.5}$ and are

29   even better surrogates for daily personal exposures to ambient $PM_{2.5}$. Thus, in a multiple

30   regression using PM and a gaseous copollutant, both variables would be surrogates for personal

31   exposure to ambient PM.

1   Sarnat et al. (2001) point out that "it is inappropriate to treat one variable as a confounder

2   of another when both variables are actually surrogates of the same thing." While the exposure

3   results from these studies are based on a small number of non-randomly chosen subjects and

4   therefore cannot be extrapolated with assurance to other situations, they do indicate the value of

5   exposure analysis in identifying which of several collinear variables could possibly be causal.

6   The work also suggests that neither NO_2, O_3, nor SO_2 are likely to be the causal factor in the

7   reported associations of ambient PM with health effects. No information was found on the

8   correlation of ambient CO with personal exposure to CO in homes with no indoor CO sources.

9   However, the low spatial homogeneity of ambient CO concentrations suggests that the

10   relationship would be weak. Therefore, it seems likely, but not certain, that exposure

11   relationships would also indicate that CO is unlikely to be a contributor to the health effects

12   attributed to PM. It is important to understand that this does not indicate that these ambient

13   pollutants do not cause health effects of the type associated with PM in epidemiologic analyses.

14   It only indicates that community, time-series epidemiology using ambient concentrations cannot

15   provide information on the possible health effects of pollutants whose ambient concentrations are

16   not significantly correlated with personal exposure to that ambient pollutant.

17   Sarnat et al. (2001) also suggest that some of the gaseous co-pollutants may be acting as

18   surrogates for specific $PM_{2.5}$ source categories or components. "For subjects with COPD,

19   ambient CO and NO_2 were not significantly associated with total personal $PM_{2.5}$, but were

20   significantly associated with personal exposure to $PM_{2.5}$ of ambient origin and also to personal

21   elemental carbon (EC). These significant associations may be due to the fact that motor vehicles

22   are a major source of CO, NO_2, EC, and, to a lesser degree, to $PM_{2.5}$ of ambient origin.

23   Conversely, ambient CO and NO_2 were not significantly associated with personal sulfate, a

24   pollutant not associated with motor vehicle emissions. O_3, in contrast, was predominantly

25   associated with personal sulfate (positively in summer and negatively in winter) . . ." Thus, CO,

26   NO_2, EC, and $PM_{2.5}$ may be surrogates for personal exposure to pollutants from motor vehicles

27   and O_3 may be a surrogate for regional sulfate. It should be noted that since $PM_{2.5}$, CO, NO_2, EC,

28   and PM associated with motor vehicles are all significantly correlated with each other, a

29   community, time-series epidemiologic analysis, in one community for one time period, cannot

30   tell whether a variable is actually responsible for relationship between concentration and health

31   effects observed in the analysis, or whether the variable is a surrogate for the causal variable.

1   In order to more clearly differentiate between contributor and surrogate, it will be necessary to

2   integrate information from toxicology and exposure analysis, as well as from epidemiologic

3   studies in different time periods and different communities.

4

9.6.5 Summary

6   For most cities, site-to-site correlations are high for $PM_{2.5}$. However, the spatial

7   distribution of PM should be investigated before beginning long term monitoring for exposure or

8   epidemiologic studies. The relationship between the concentrations of an ambient pollutant

9   outdoors and the contribution of that ambient pollutant to personal exposure is given by the mass

10   balance model (Equation 9-2) and depends on the outdoor concentration, the time spent outdoors

11   and indoors, the air exchange rate, and penetration factor, and the indoor deposition or removal

12   rate. For a given PM component, the major cause of variability in the relationship is the air

13   exchange rate. For gaseous co-pollutants, if the correlation between the ambient concentrations

14   and the personal exposures to the ambient concentrations are not statistically significant, that

15   gaseous co-pollutant cannot contribute to the health effect attributed to PM in a community,

16   time-series epidemiologic analysis. However, if ambient concentration of the gaseous

17   co-pollutant is significantly correlated with the ambient concentration of PM, it may be as good

18   or better indicator of personal exposure to the toxicologically active component of PM as the

19   ambient PM concentration; and, thus, it may be a surrogate, i.e., it will falsely show an effect due

20   to its correlation with the personal exposure to the active component and, in a multiple

21   regression, it will appear to reduce the effect associated with PM. Therefore, correlations among

22   ambient concentrations and ambient concentration-personal exposure relationships for PM and

23   co-pollutants are useful in interpreting the results of epidemiologic studies.

24

25

9.7 EXPOSURE TO BIOLOGICALLY IMPORTANT CHARACTERISTICS OF PARTICULATE MATTER

28   *What are the exposures to biologically important constituents and specific characteristics*

29   *of particulate matter that cause responses in potentially susceptible subpopulations and the*

30   *general population?*

31

1   In their discussion of Topic 2, the NRC notes that in order to make such investigations

2   practicable, it will be necessary to characterize susceptible subpopulations more fully, identify

3   toxicologically important chemical constituents or particle-size fractions, develop and field-test

4   exposure-measurement techniques for relevant properties of PM, and design comprehensive

5   studies to determine population exposures.

6

9.7.1 Exposure Relationships for Susceptible Subpopulations

8   Children, the elderly, and people with pre-existing diseases such as diabetes, respiratory

9   disease, and cardiovascular disease appear to constitute susceptible subpopulations. A number of

10   studies of small cohorts drawn from these and other subpopulations have been conducted

11   recently by EPA and other organizations. Correlations between ambient concentrations and total

12   personal exposure have been presented for a few of these. However, most of the studies have not

13   yet been published, most of the studies have not reported the ambient exposure, and the studies

14   have not been analyzed to determine if there are indeed exposure differences between susceptible

15   groups and the general population.

16   An analysis of cohort exposure studies available in 1998 (Wallace, 2000) concluded that

17   the personal cloud component of nonambient exposure was less for subjects with COPD than for

18   the general population, healthy elderly subjects or children, presumably because of the higher

19   activity level of younger or healthier subjects. However, the relationship between ambient

20   concentrations and personal exposure for COPD patients was not better than that for other

21   cohorts. Wallace (2000) noted that the desirable correlation is that "between personal exposure

22   to particles *originating outdoors* and outdoor concentrations." However, at that time there was

23   no information on the ambient component of personal exposure. Unfortunately, there is still no

24   published information that would suggest differences in exposure relationships for healthy versus

25   susceptible populations.

26

9.7.2 Toxicologically Important Components of PM

28   Inherent in the NRC research agenda (NRC, 1998) was the consideration that one, or

29   perhaps a few, characteristics of PM would be associated with toxicity, and exposure monitoring

30   could concentrate on these components. However, it has not yet been possible to identify any

1 PM characteristic as not being of toxicologic importance. Table 9-7 lists characteristics of PM

2 that have been found to be associated with toxicity either through epidemiologic or toxicologic

3 studies.

4

5

TABLE 9-7. PARTICULATE MATTER CHARACTERISTICS POTENTIALLY RELEVANT TO HEALTH

Particle number

Particle surface area

Mass-ultrafine PM [$PM_{0.1}$]

Mass-fine PM [$PM_{2.5}$ or $PM_{1.0}$]

Mass-thoracic coarse PM [$PM_{10-2.5}$ or PM_{10-1}]

Sulfate

Strong acidity (H^+)

Nitrate

Elemental carbon

Organic carbon (many different compounds)

Transition metals

Specific toxic metals

Bioaerosols

9.7.3 Exposure-Measurement Techniques

2 Measurement techniques, suitable for stationary monitors with 24-hour collection periods,

3 exist for the characteristics of PM listed in Table 9-7. For many of these measurements,

4 continuous or 1-hour-average stationary monitors also exist or are in development. However,

5 personal monitoring is usually limited to either $PM_{2.5}$ or PM_{10}. A few studies have included

6 passive monitors for NO_2, O_3, SO_2, and CO. A roll-around monitor, which can be rolled around

7 to follow a person and thus simulate a personal exposure measurement with a more complete

1   suite of measurements, has been used in recent studies. However, with the exception of personal

2   light-scattering monitors, which do not have well-established relationships with PM mass, there

3   are still no adequate personal monitors for continuous measurement of mass of other PM

4   characteristics.

5

6   ## 9.7.4 Comprehensive Studies to Determine Population Exposure

7   Chapter 5 reports only four exposure studies that have even attempted to provide

8   statistically representative studies of population exposure of the general population or susceptible

9   subgroups. However, only in the case of the PTEAM study has the exposure data been used to

10   estimate ambient and nonambient exposure separately (for PM_{10}). Even though statistically

11   representative studies are limited, available data from small cohorts allow some inferences

12   regarding differences in concentration-exposure relationships among different characteristics of

13   PM. PM may be classified by particle size, by chemical composition, or by sources.

14   Concentration - exposure relationships may be different for different classes of particles.

15

16   **Central Site to Outdoors**

17   The 1996 PM AQCD reported information from a few cities (mostly eastern US) that

18   suggested that site-to-site correlation coefficients, r, were high for sulfate and $PM_{2.5}$ in some

19   cities; were lower but still relatively high for PM_{10} and TSP; but were low for $PM_{10-2.5}$ (Figure

20   9-17). However, there was little information on site-to-site correlations of chemical components

21   of PM (except sulfate and strong acidity) or of orthogonal source-category factors. New site-to-

22   site correlation studies, using PM data from the AIRS data base, are presented in Chapter 3.

23   Some examples of the differences in site-to-site correlations for $PM_{2.5}$ and $PM_{10-2.5}$, derived from

24   the data in Chapter 3, are shown in Figure 9-18. It should be noted that the $PM_{2.5}$ data is from

25   1999 and 2000 and satisfies certain criteria for number of days of data per season. The $PM_{10-2.5}$

26   data is from 2000 only and is less complete. In addition, some information on the site-to-site

27   correlations of $PM_{2.5}$ components and source contributions are now available (Figures 9-19 and

28   9-20). In order to reduce spatial variability, some cohort studies have used the concentration at

29   the nearest monitoring site or the distance to major traffic sources for exposure information.

30

31
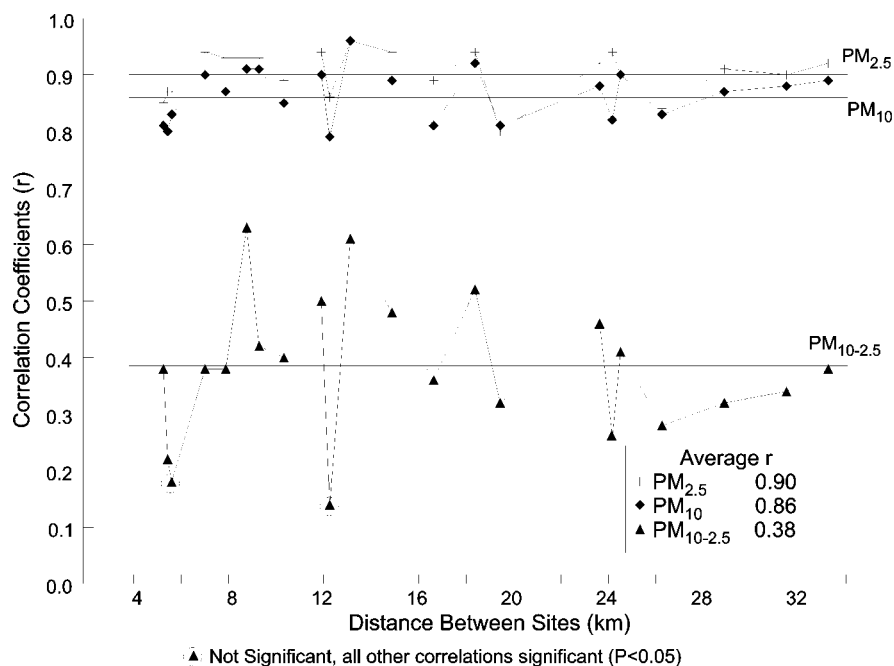
Figure 9-17. Spatial variation of PM$_{2.5}$, PM$_{10}$, and PM$_{10-2.5}$ as shown by site-to-site correlation coefficients as a function of distance between sites for summer 1992 and 1993 in Philadelphia, PA.

Source: Wilson and Suh (1997)
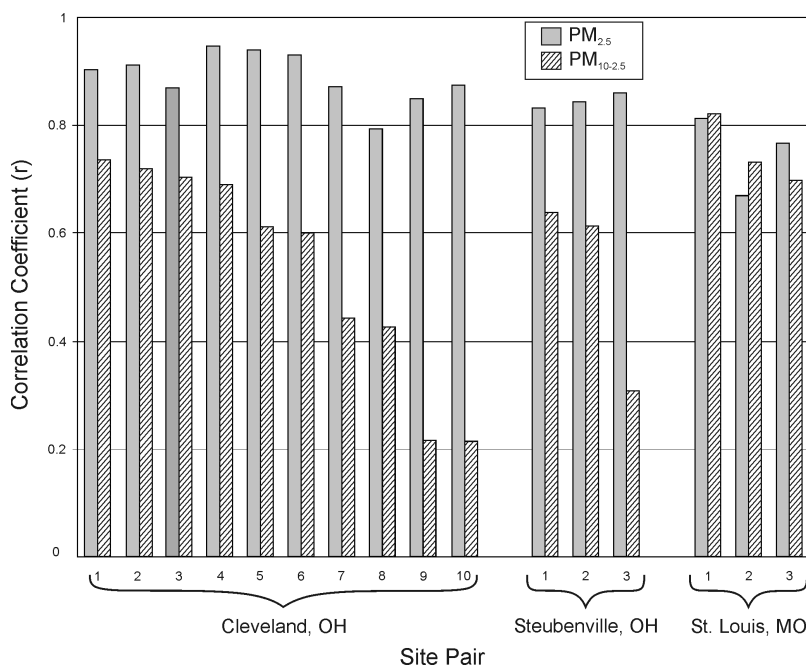
Figure 9-18. Comparison of site-to-site correlation coefficients for PM$_{2.5}$ and PM$_{10-2.5}$ for several cities. (PM$_{2.5}$ [1999 and 2000] and PM$_{10-2.5}$ [2000 only] measured at the same sites, but PM$_{10-2.5}$ data less complete.
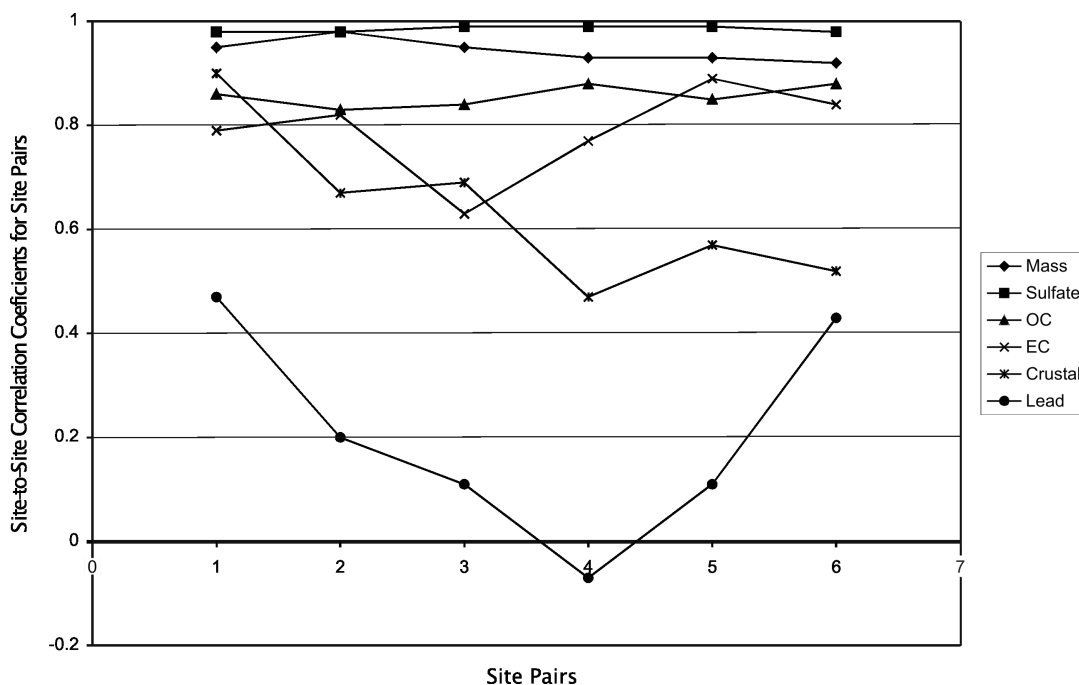
Figure 9-19. Site-to-site correlation coefficients for PM$_{2.5}$ mass and some chemical components of PM$_{2.5}$ in 1994 in Philadelphia, PA.

Source: Pinto et al. (1995).
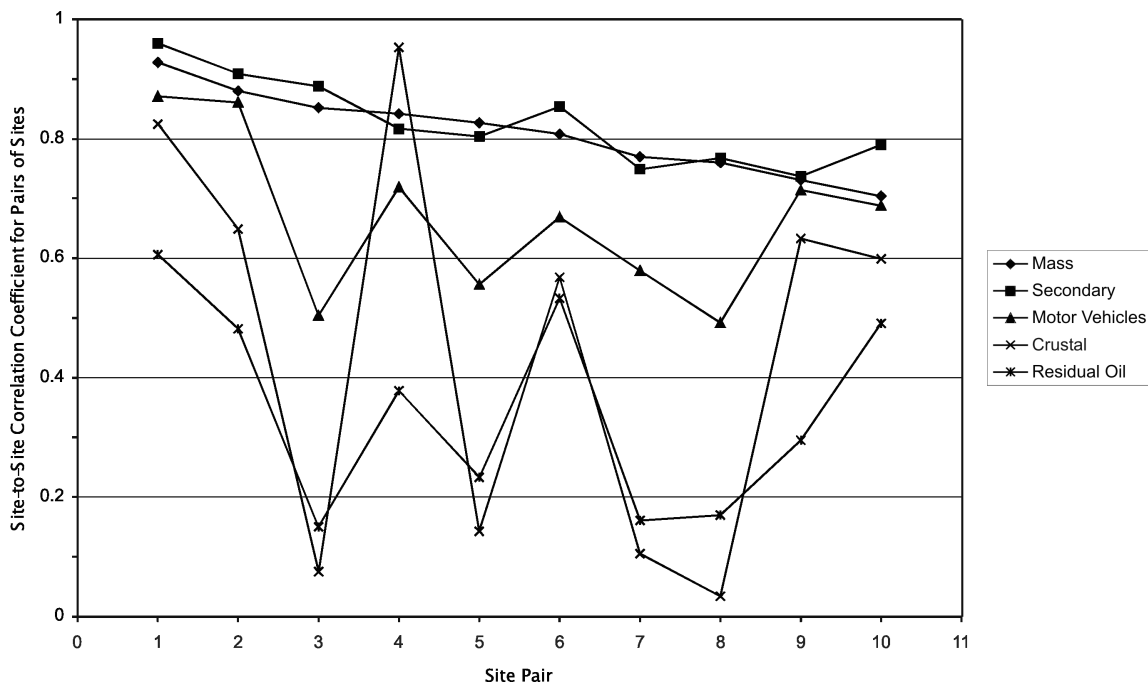
Figure 9-20. Site-to-site correlation coefficients for PM$_{2.5}$ mass and several source category factors in 1986 in the South Coast Basin (Los Angeles area).

Source: Wongphatarakul et al. (1998)

Outdoors to Indoors

1

2   Information on the infiltration rate, F_{INF}, as a function of particle size may be obtained as

3   follows. Indoor and outdoor measurements of PM concentrations as a function of particle size

4   are made during the night when it is assumed that there are no indoor activities occurring that

5   might generate indoor PM. Under this assumption the indoor concentration measurement is

6   *C(AI)* and *C(AI)/C* = F_{INF} (Long et al., 2000). As can be seen in Figure 9-21, F_{INF} is low for

7   ultrafine and coarse particles but high for accumulation mode particles. F_{INF} also depends on the

8   air exchange rate, *a*, F_{INF} increases when *a* increases. The variation of *P* and *k* as a function of

9   particle size can also be determined by this technique (Figure 9-22) (Long et al., 2000). There is

10   little information on ambient concentration - exposure relationships for specific chemical

11   components, except sulfate, or for specific source categories, other than what would be inferred

12   from the size distributions. Infiltration ratios are low for components like strong acidity (H^+) that

13   are neutralized by indoor-generated ammonia or like ammonium nitrate (NH_4NO_3) that evaporate

14   indoors.

15
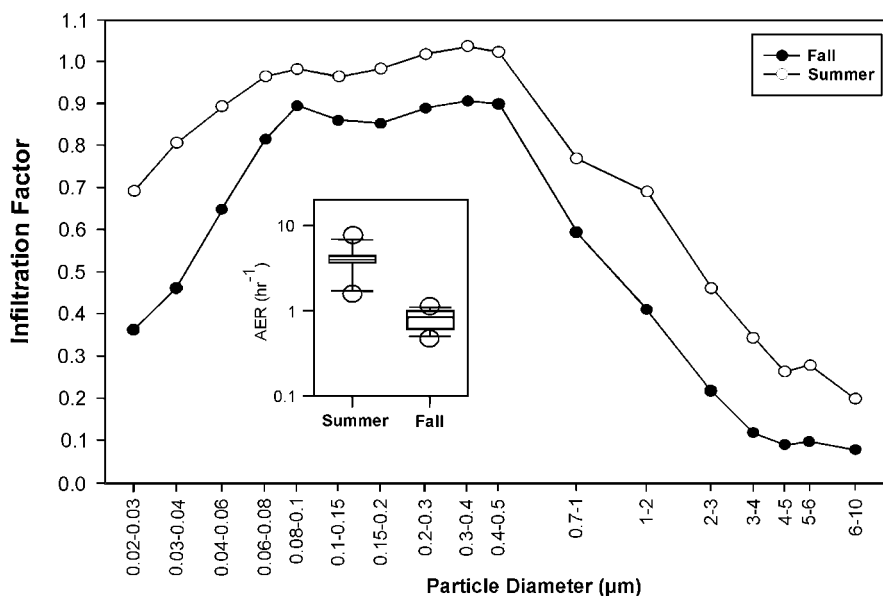
Source: Long, Suh and Koutrakis (2000)

Figure 9-21. Values of geometric mean infiltration factor, F_{INF} = A/C, as a function of particle diameter for hourly nighttime data (assuming no indoor sources) for summer and fall seasons. Distribution of air exchange rates, *a*, for each season are shown in the insert.

Source: Long et al. (2000).
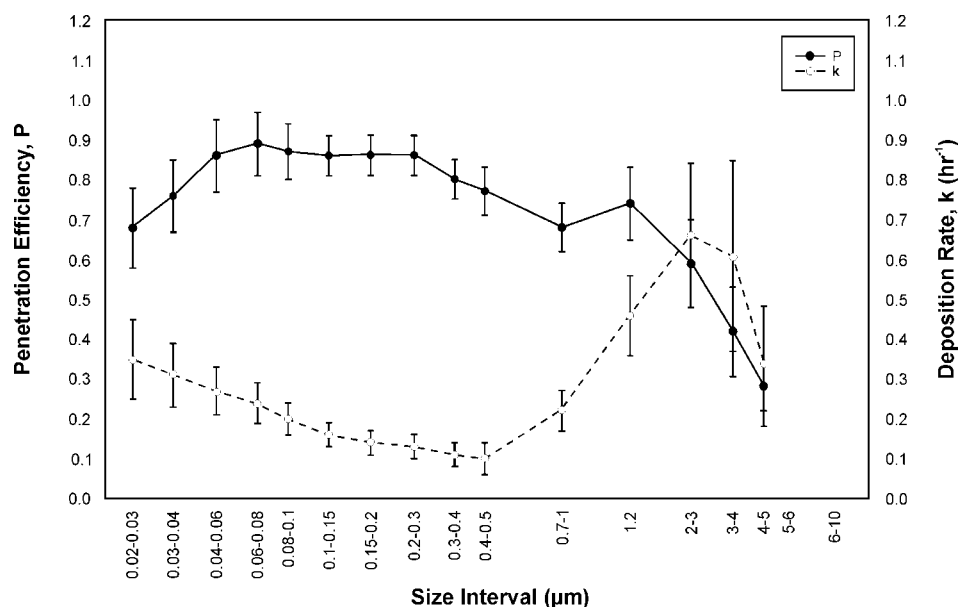
Figure 9-22. **Values of penetration efficiency and deposition rate as a function of particle diameter estimated from model of average nighttime indoor-outdoor concentration data.**

Source: Long et al. (2000).

9.7.5 Air Pollutants Generated Indoors

The NRC discussion of Research Topic 2 is clear that the primary purpose of the investigations recommended should be "to examine the outdoor contributions to measurements of total personal exposure." However, they also recommended determining the exposure to "air pollutants generated indoors." Total personal exposure includes both ambient and nonambient sources. Important sources of indoor PM are smoking, cooking, and cleaning. Because of the variation of F_{inf} with particle size, ambient-infiltrated PM tends to be primarily in the accumulation mode. As shown in Table 9-8, however, indoor PM is generated primarily in the ultrafine mode (smoking, other combustion sources, most cooking) or the coarse mode (cleaning, sauteing). Another, possibly important indoor source, is the reaction of ambient-infiltrated ozone with indoor emissions of terpenes from air fresheners or cleaning agents, e.g., cleaning with Pine Sol. These particles are also generated largely in the ultrafine mode. Ambient and indoor generated PM also differ somewhat in their chemical composition as shown in Table 9-9.

TABLE 9-8. VOLUME MEAN DIAMETER (VMD) OF INDOOR PARTICLE SOURCES [a,b]

Particle Source	N	Indoor Activity - Mean VMD (μm)
Cooking		
Baking (Electric)	8	0.189
Baking (Gas)	24	0.107
Toasting	23	0.138
Broiling	4	0.114
Stir-Frying	3	0.135
Frying	20	0.173
Barbecuing	2	0.159
Sautéing, fine	13	0.184
Sautéing, coarse	13	3.48
Cleaning		
Dusting	11	5.38
Vacuuming	10	3.86
Cleaning with Pine Sol	5	0.097
General Activities		
Walking Vigorously (w/Carpet)	15	3.96
Sampling w/Carpet	52	4.25
Sampling w/o Carpet	26	4.28
Burning Candles	7	0.311

Notes:

Includes only individual particle events that were unique for a given time period and could be detected above background particle levels.

Fine particle sizes calculated for $PV_{0.02-0.5}$ using SMPS data; coarse particle sizes calculated for $PV_{0.7-10}$ using APS data.

Source: Long et al. (2000).

TABLE 9-9. CONCENTRATION DIFFERENCES BETWEEN CONSTITUENTS OF NONAMBIENT (INDOOR-GENERATED) AND AMBIENT PM

Higher Concentration in Nonambient PM	*Higher Concentration in Ambient PM*
Mold Spores	Pollen
Endotoxin	Transition Metals (non-soil Fe, Mn)
Animal Dander	Other Metals (Se, As, Ni, Cu)
Biological Fragments (from insects, etc)	Oxygenated and Nitrated Polyaromatic Compounds
Environmental Tobacco Smoke	Other Oxygenated Organic Compounds
Resuspended Soil and House Dust	Sulfates and Nitrates
Ultrafine Particles and Coarse-Mode Particles	Accumulation-Mode Particles

9.8 DOSIMETRY: DEPOSITION AND FATE OF PARTICLES IN THE RESPIRATORY TRACT

What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Knowledge of the dose of particles delivered to a target site or sites in the respiratory tract is important for understanding possible health effects associated with human exposure to ambient PM and for extrapolating and interpreting data obtained from studies of laboratory animals. The dosimetry of particles of different sizes are subject to large differences in regional respiratory tract deposition, translocation, and clearance mechanisms and pathways and, consequently, retention times. The following sections summarize the current understanding of the physical characteristics of particles and the biological determinants that affect particle dosimetry mechanisms and pathways, as discussed in Chapter 6.

9.8.1 Particle Deposition in the Respiratory Tract

For dosimetry purposes, the respiratory tract can be divided into three regions: (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists of head airways (i.e., nasal and oral passages) through the larynx and represents the areas through which inhaled air first passes. In humans, inhalation can occur through the nose or mouth (or

1　both, known as oronasal breathing). However, most laboratory animals commonly used in

2　respiratory toxicological studies are obligate nose breathers.

3　　　From the ET region, inspired air enters the TB region at the trachea. From the level of the

4　trachea, the conducting airways then undergo branching for a number of generations. The

5　terminal bronchiole is the most peripheral of the distal conducting airways and these lead,

6　in humans, to the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (all of which

7　comprise the A region). All of the conducting airways, except the trachea and portions of the

8　mainstem bronchi, are surrounded by parenchymal tissue. This is composed primarily of the

9　alveolated structures of the A region and associated blood and lymphatic vessels. It should be

10　noted that the respiratory tract regions are comprised of various cell types and that there are

11　distinct differences in the cells of airway surfaces in the ET, TB, and A regions.

12　　　Particles deposit in the respiratory tract by five mechanisms: (1) inertial impaction,

13　(2) sedimentation, (3) diffusion, (4) electrostatic precipitation, and (5) interception. Sudden

14　changes in airstream direction and velocity cause inhaled particles to impact onto airway

15　surfaces. The ET and upper TB airways are dominant sites of inertial impaction, a key

16　mechanism for particles with aerodynamic diameter $(D_a) > 1 \, \mu$m. Particles with $D_a > 0.5 \, \mu$m

17　mostly are affected by sedimentation out of the airstream. Both sedimentation and inertial

18　impaction influence deposition of particles in the same size range and occur in the ET and TB

19　regions, with inertial impaction dominating in the upper airways and gravitational settling

20　(sedimentation) increasingly more dominant in lower conducting airways. Particles with actual

21　physical diameters $< 1 \, \mu$m are increasingly subjected to diffusive deposition due to random

22　bombardment by air molecules, resulting in contact with airway surfaces. Particles between

23　0.3 and 0.5 μm in size are small enough to be little influenced by impaction or sedimentation and

24　large enough to be minimally influenced by diffusion, and so, they undergo the least respiratory

25　tract deposition. The interception potential of any particle depends on its physical size; fibers are

26　of chief concern for interception, their aerodynamic size being determined mainly by their

27　diameter. Electrostatic precipitation is deposition related to particle charge; effects of charge on

28　deposition are inversely proportional to particle size and airflow rate. This type of deposition is

29　likely small compared to effects of other deposition mechanisms and is generally a minor

30　contributor to overall particle deposition, but one recent study found it to be a significant TB

31　region deposition mechanism for ultrafine, and some fine, particles.

1   The ET region acts as an efficient filter that reduces penetration of inhaled particles to the

2   TB and A regions of the lower respiratory tract. Total respiratory tract deposition increases with

3   particle size for particles >1.0 μm D_a, is at a minimum for particles 0.3 to 0.5 μm, and increases

4   as particle size decreases below that range. The ET deposition is higher with nose breathing than

5   for mouth breathing, with increased ventilation rates associated with increasing levels of physical

6   activity or exercise leading to more oronasal breathing and increased delivery of inhaled particles

7   to TB and A regions in the lung.

8   Hygroscopicity, the propensity of a material for taking up and retaining moisture, is a

9   property of some ambient particle species and affects respiratory tract deposition. Such particles

10   can increase in size in humid air in the respiratory tract and, when inhaled, deposit according to

11   their hydrated size rather than their initial size. Compared to nonhygroscopic particles of the

12   same initial size, deposition of hygroscopic aerosols in different regions varies, depending on

13   initial size: hygroscopicity generally increases total deposition for particles with initial sizes

14   larger than $\approx$0.5 μm, but decreases deposition for particles between $\approx$0.01 and 0.5 and again

15   increases deposition for particles <0.01 μm.

16   Enhanced particle retention occurs on carinal ridges in the trachea and throughout the

17   segmental bronchi; and deposition "hot spots" occur at airway bifurcations or branching points.

18   Peak deposition sites shift from distal to proximal sites as a function of particle size, with greater

19   surface dose in conducting airways than in the A region for all particle sizes. Whereas both fine

20   ($\leq$2.5 μm) and thoracic coarse (2.5 to 10 μm) particles deposit to about the same extent on a

21   percent particle mass basis in the trachea and upper bronchi, a distinctly higher percent of fine

22   particles deposit in the A region. However, surface number dose (particles/cm^2/day) is much

23   higher for fine than for coarse particles, indicating much higher numbers of fine particles

24   depositing, with the fine fraction contributing upwards of 10,000 times greater particle number

25   per alveolar macrophage.

26   Ventilation rate, gender, age, and respiratory disease status are all factors that affect total

27   and regional respiratory tract particle deposition. In general, because of somewhat faster

28   breathing rates and likely smaller airway size, women have somewhat greater deposition of

29   inhaled particles than men in upper TB airways, but somewhat lower A region deposition than

30   for men. Children appear to show four effects: (1) greater total respiratory tract deposition than

31   adults (possibly as much as 50% greater for those <14 years old than for adults >14 years),

1   (2) distinctly enhanced ET region deposition (decreasing with age from 1 year), (3) enhanced TB

2   deposition for particles < 5 μm, and (4) enhanced A region deposition (also decreasing with age).

3   Overall, given that children have smaller lungs and higher minute volumes relative to lung size,

4   they likely receive greater doses of particles per lung surface area than adults for comparable

5   ambient PM exposures. This and the propensity for young children to generally exhibit higher

6   activity levels and associated higher breathing rates than adults likely contribute to enhanced

7   susceptibility to ambient particle effects resulting from particle dosimetry factors. In contrast,

8   limited available data on respiratory tract deposition across adult age groups (18 to 80 years) with

9   normal lung function do not indicate age-dependent effects (e.g., enhanced deposition in healthy

10 elderly adults). Altered PM deposition patterns due to respiratory disease status may put certain

11 groups of adults (including some elderly) and children at greater risk for PM effects.

12   Both information noted in the 1996 PM AQCD and newly published findings discussed in

13 this document indicate that respiratory disease status is an especially important determinant of

14 respiratory tract particle deposition. Importantly, the pathophysiologic characteristics of chronic

15 obstructive pulmonary disease (COPD) contribute to more heterogenous deposition patterns and

16 differences in regional deposition. One study indicates that people with COPD tend to breath

17 faster and deeper than those with normal lungs (i.e., about 50% higher resting ventilation) and

18 had about 50% greater deposition than age-matched healthy adults under typical breathing

19 conditions, with average deposition rates 2.5 times higher under elevated ventilation rates.

20 Enhanced deposition appears to be associated more with the chronic bronchitic than the

21 emphysematous component of COPD. In this and other new studies, fine-particle deposition

22 increased markedly with increased degree of airway obstruction (ranging up to 100% greater with

23 severe COPD). With increasing airway obstruction and uneven airflow because of irregular

24 obstruction patterns, particles tend to penetrate more into remaining better ventilated lung areas,

25 leading to enhanced focal deposition at airway bifurcations and alveoli in those A region areas.

26 In contrast, TB deposition increases with increasingly more severe bronchoconstrictive states, as

27 occur with asthmatic conditions.

28   Differences between species in particle deposition patterns were summarized in the 1996

29 PM AQCD and more recently by Schlesinger et al. (1997), as discussed in Chapter 6 of this

30 document. These differences should be considered when relating biological responses obtained

31 in laboratory animal studies to effects in humans. Various species used in inhalation toxicology

1   studies serving as the basis for dose-response assessment may not receive identical doses in a
2   comparable respiratory tract region (i.e., ET, TB, A) when exposed to the same aerosol at the
3   same inhaled concentration. This is illustrated by mathematical modeling studies that evaluate
4   interspecies differences in respiratory tract deposition. For example, Hofmann et al. (1996)
5   found total deposition efficiencies for all particles (0.01, 1, and 10 μm) at upper and lower
6   airway bifurcations to be comparable for rats and humans, but when higher penetration
7   probabilities from preceding airways in the human lung were considered, bronchial deposition
8   fractions were mostly higher for humans. For all particle sizes, deposition at rat bronchial
9   bifurcations was less enhanced on the carinas than in human airways. Numerical simulations of
10   three-dimensional particle deposition patterns within selected (species-specific) bronchial
11   bifurcations indicated that interspecies differences in morphologic asymmetry is a major
12   determinant of local deposition patterns. The dependence of deposition on particle size is similar
13   in rats and humans, with deposition minima in the 0.1- to 1-μm size range for both total
14   deposition and deposition in the TB and A regions, but total respiratory tract and TB deposition
15   was consistently higher in the human lung. Alveolar regional deposition in humans was lower
16   than in rat for 0.001- to 10-μm particles (deposition of such particles being highest in the upper
17   bronchial airways), whereas it was higher for 0.1- and 1-μm particles in more peripheral airways
18   (i.e., bronchiolar airways in rat, respiratory bronchioles in humans). In a histology study, Nikula
19   et al. (2000) examined particle retention in rats (exposed to diesel soot) and humans (exposed to
20   coal dust). In both, the volume density of deposition increased with increasing dose. In rats,
21   diesel exhaust particles were found mainly in lumens of the alveolar duct and alveoli, whereas in
22   humans, retained dust was mainly in interstitial tissue. Thus, in the two species, different lung
23   cells appear to contact retained particles and may result in different biological responses with
24   chronic exposure.
25   The probability of any biological effect of PM in humans or animals depends on particle
26   dosimetry, and subsequent particle retention, as well as underlying dose-response relationships.
27   Interspecies dosimetric extrapolation must, therefore, consider differences in deposition,
28   clearance, translocation, and dose-response. Even similar deposition patterns may not result in
29   similar effects in different species, because dose also is affected by clearance mechanisms and
30   species sensitivity. Total number of particles deposited in the lung may not be the most relevant
31   dose metric by which to compare species; rather, the number of deposited particles per unit

1 surface area may determine response. Even if deposition is similar in rats and humans, there

2 would be a higher deposition density in the rat because of the smaller surface area of the rat lung.

3 Thus, species-specific differences in deposition density are important when attempting to

4 extrapolate health effects observed in laboratory animals to humans.

5

6 **9.8.2 Particle Clearance and Translocation**

7 Particles depositing on airway surfaces may be cleared from the respiratory tract completely

8 or translocated to other sites within this system by regionally specific clearance mechanisms, as

9 follow: *ET region*—mucocialiary transport, sneezing, nose wiping and blowing, and dissolution

10 and absorption into blood; *TB region*—mucociliary transport, endocytosis by macrophages and

11 epithelial cells, coughing, and dissolution and absorption into blood and lymph; *A region*—

12 macrophages, epithelial cells, interstitial, and dissolution and absorption into blood and lymph.

13 Regionally specific clearance defense mechanisms operate to clear deposited particles of

14 varying particle characteristics (size, solubility, etc.) from the ET, TB, and A regions and are

15 variously affected by different disease states. For example, particles are cleared from the ET

16 region by mucociliary transport to the nasopharynx area, dissolution and absorption into the

17 blood, or sneezing, wiping or blowing of the nose; but such clearance is slowed by chronic

18 sinusitis, bronchiectasis, rhinitis, and cystic fibrosis. Also, in the TB region, poorly soluble

19 particles are cleared mainly by upward mucociliary transport or by phagocytosis by airway

20 macrophages that move upward on the mucociliary blanket, followed by swallowing. Soluble

21 particles in the TB region are absorbed mostly into the blood and some by mucociliary transport.

22 Although TB clearance is generally fast and much material is cleared in <24 h, the slow

23 component of TB clearance (likely associated with bronchioles <1-mm diameter) results in

24 upwards of 40 to 50% of deposited 6- to 10-μm particles being retained for >24 h and clearance

25 half-times of about 50 days. Bronchial mucous transport is slowed by bronchial carcinoma,

26 chronic bronchitis, asthma, and various acute respiratory infections; these are disease conditions

27 that logically would be expected to increase retention of deposited particle material and, thereby,

28 increase the probability of toxic effects from inhaled ambient PM components reaching the TB

29 region. Also, spontaneous coughing, an important TB region clearance mechanism, does not

30 appear to fully compensate for impaired mucociliary clearance in small airways and may become

31 depressed with worsening airway disease, as seen in COPD.

1   Clearance of particles from the A region by alveolar macrophages and their mucociliary

2   transport is usually rapid (<24 h). However, penetration of uningested particles into the

3   interstitium increases with increasing particle load and results in increased translocation to lymph

4   nodes. Soluble particles not absorbed quickly into the blood stream and translocated to

5   extrapulmonary organs (e.g., the heart) within minutes may also enter the lymphatic system, with

6   lymphatic translocation probably being increased as other clearance mechanisms (e.g., removal

7   by macrophages) are taxed or overwhelmed under "particle overload" conditions. Insoluble

8   particles <2 μm clear to the lymphatic system at a rate independent of size; particles of this size,

9   more so than those >5.0 μm, are deposited significantly in the A region. Translocation into the

10   lymphatic system is quite slow, and elimination from lymph nodes even slower (half-times

11   estimated in decades). Focal accumulations of reservoirs of potentially toxic materials and their

12   slow release for years after initial ambient PM exposure may account partially for the observation

13   in epidemiologic studies that higher relative risks are associated with long-term ambient PM

14   exposure than can be accounted for by additive effects of acute PM exposures. Alveolar region

15   clearance rates are decreased in human COPD sufferers and slowed by acute respiratory

16   infections, and the viability and functioning of alveolar macrophages are reduced in human

17   asthmatics and in animals with viral lung infections. These observations suggest that persons

18   with asthma or acute lung infections are likely at increased risk for ambient PM exposure effects.

19   Differences in regional and total clearance rates between some species reflect differences in

20   mechanical clearance processes. The importance of interspecies clearance differences is that

21   retention of deposited particles can differ between species and may result in differences in

22   response to similar PM exposures. Hsieh and Yu (1998) summarize existing data on pulmonary

23   clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and

24   human. Two clearance phases, "fast" and "slow," in the A region are associated with mechanical

25   clearance along two pathways, the former with the mucociliary system and the latter with lymph

26   nodes. Rats and mice are fast clearers, compared to other species. Increasing initial lung burden

27   results in an increasing mass fraction of particles cleared by the slower phase. As lung burden

28   increases beyond 1 mg particles/g lung, the fraction cleared by the slow phase increases to almost

29   100% for all species. The rate for the fast phase is similar in all species, not changing with

30   increasing lung burden, whereas the slow phase rate decreases with increasing lung burden.

31   At elevated burdens, the "overload" effect on clearance rate is greater in rats than in humans.

9.8.3 Deposition and Clearance Patterns of Particles Administered by Inhalation Versus Intratracheal Instillation

Inhalation is the most directly relevant exposure route for evaluating PM toxicity, but many studies deliver particles by intratracheal instillation. Because particle disposition is a determinant of dose, it is important to compare deposition and clearance of particles delivered by instillation versus inhalation. It is difficult to compare particle deposition and clearance among different inhalation and instillation studies because of differences in experimental methods and in quantification of particle deposition and clearance. Key points from a recent detailed evaluation (Driscoll et al., 2000) of the role of instillation in respiratory tract dosimetry and toxicology studies are informative. In brief, inhalation may result in deposition within the ET region, the extent of which depends on the size of the particles used, but intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly to the TB tree. Although some studies indicate that short (0 to 2 days) and long (100 to 300 days postexposure) phases of clearance of insoluble particles delivered either by inhalation or intratracheal instillation are similar, others indicate that the percent retention of particles delivered by instillation is greater than for inhalation, at least up to 30 days postexposure. Another salient finding is that inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs, but instillation is typified by heterogeneous distribution (especially in the A region) and high levels of focal particles. Most instilled material penetrates beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of particles. This difference is reflected in particle burdens within macrophages, those from animals inhaling particles being burdened more homogeneously and those from animals with instilled particles showing some populations of cells with no particles and others with heavy burdens, and is likely to impact clearance pathways, dose to cells and tissues, and systemic absorption. Exposure method, thus, clearly influences dose distribution that argues for caution in interpreting results from instillation studies.

9.8.4 Inhaled Particles as Potential Carriers of Toxic Agents

It has been proposed that particles also may act as carriers to transport toxic gases into the deep lung. Water-soluble gases, which would be removed by deposition to wet surfaces in the upper respiratory system during inhalation, could dissolve in particle-bound water and be carried with the particles into the deep lung. Equilibrium calculations indicate that particles do not

1   increase vapor deposition in human airways. However, these calculations do show that soluble

2   gases are carried to higher generation airways (deeper into the lung) in the presence of particles

3   than in the absence of particles. In addition, species such as SO_2 and formaldehyde react in

4   water, reducing the concentration of the dissolved gas-phase species and providing a kinetic

5   resistence to evaporation of the dissolved gas. Thus, the concentration of the dissolved species

6   may be greater than that predicted by the equilibrium calculations. Also, certain other toxic

7   species (e.g., nitric oxide [NO], nitrogen dioxide [NO_2], benzene, polycyclic aromatic

8   hydrocarbons [PAH], nitro-PAH, a variety of allergens) may be absorbed onto solid particles and

9   carried into the lungs. Thus, ambient particles may play important roles not only in inducing

10   direct health impacts of their constituent components but also in facilitating delivery of toxic

11   gaseous pollutants or bioagents into the lung and may, thereby, serve as key mediators of health

12   effects caused by the overall air pollutant mix.

13

14   9.8.5 Summary of Particle Dosimetry

15   Although the current understanding of basic mechanisms of particle dosimetry, clearance,

16   and retention has not changed since the 1996 PM AQCD, additional information has become

17   available on the role of certain biological determinants of these processes, such as gender and

18   age; and there has been an expansion of previous knowledge about the relationship between

19   regional deposition and translocation in regard to specific particle size ranges of significance to

20   ambient particulate exposure scenarios. There also has been significant improvement in the

21   mathematical and computational fluid dynamic modeling of particle dosimetry in the respiratory

22   tract of humans. Although the models have become more sophisticated and versatile, validation

23   of the models is still needed.

24   One of the areas that has improved since the 1996 PM ACQD is consideration of specific

25   and relevant ambient size particle ranges in deposition studies. One such size mode is the nuclei

26   mode or ultrafine particles ($< 0.1\ \mu$m). While further information on respiratory deposition for

27   this size mode is still needed, there has been an improvement in the understanding of total

28   deposition as a function of particle size and breathing pattern and of certain aspects of regional

29   deposition of ultrafine particles. This new information indicates that the ET region, especially

30   the nasal passages, is a very efficient "filter" for these particles, reducing the amount which

31   would be available for deposition in the TB and A regions of the respiratory tract. Within the

1   thoracic region, the deposition distribution of ultrafine particles is highly skewed towards the

2   proximal airway regions and resembles that of coarse particles. In other words, deposition

3   patterns of ultrafine particles are very much like those of coarse particles. Another example

4   involves studies which attempt to evaluate the contribution of fine- and coarse-mode particles to

5   deposition in various parts of the respiratory tract, although there have been only a few of these.

6   It always has been clear that certain host factors affect deposition, and there has been

7   improvement since the 1996 PM AQCD in the understanding of some of these factors,

8   specifically gender, age, and health status. Recent information suggests that there are significant

9   gender differences in the homogeneity of deposition as well as the deposition rate, and this could

10   affect susceptibility. In regard to age, recent evaluations employed both mathematical models as

11   well as experimental studies, and most involved comparison of deposition in children compared

12   to adults. These studies generally indicate that children would receive greater doses of particles

13   per lung surface area than would adults. Unfortunately, deposition studies in another potentially

14   susceptible population, namely the elderly, are still lacking although there have been a number of

15   studies examining effects of chronic pulmonary disease on deposition. These studies confirmed

16   that significant increases in deposition could occur in obstructed lungs.

17   Once deposited on airway surfaces, particles are subjected to translocation and clearance.

18   While the general pathways of clearance have been known for years, recent information has

19   improved the understanding of translocation of particles within size ranges which may be of

20   specific concern for ambient exposures. One such size mode, as noted above, is the ultrafine;

21   and recent studies indicate that ultrafine particles can be rapidly cleared from the lungs into the

22   systemic circulation and reach extrapulmonary organs. This provides a mechanism whereby

23   inhaled particles may affect cardiovascular function, as noted in various epidemiological studies.

24   As with experimental studies, the major improvements in mathematical modeling of

25   dosimetry involve evaluation of realistic size modes for ambient conditions, as well as

26   improvements in the precision of these models for more realistic depictions of respiratory tract

27   airflow patterns and detailed airway structures that may result in deposition "hot spots". These

28   improvements include more detailed evaluations of enhanced deposition at airway bifurcations,

29   use of parameters that allow determination of age differences in dosimetry, and improvement in

30   the modeling of clearance mechanisms.

1   Thus, in general, while our understanding of specific aspects of particle dosimetry has

2   improved since the 1996 PM AQCD, there are still areas in need of further evaluation. These

3   include dosimetry in susceptible humans, better models for extrapolation between humans and

4   animals used in inhalation studies, and better understanding of differences in the manner in

5   which particles of different and relevant ambient size modes are handled following deposition.

6   This latter research need is important for determining the potential of various particle types to

7   exert effects systemically, rather than just locally within the respiratory tract.

8

9

9.9   ASSESSMENT OF PARTICULATE-MATTER PROPERTIES LINKED TO HEALTH EFFECTS

12   *What is the role of physicochemical characteristics of particulate matter in eliciting*

13   *adverse health effects?*

14

9.9.1 Introduction

16   Ambient PM comprises a complex mix of constituents derived from many sources, both

17   natural and anthropogenic. Hence, the physicochemical composition of PM generally reflects the

18   major contributing sources locally and regionally. Within this framework of source or origin,

19   PM composition also varies significantly by the size-mode within which it is classified (ultrafine,

20   accumulation, or coarse). It should be clear that any given particle can differ appreciably from

21   another individual particle of similar size, but that the region of origin with all of its contributing

22   sources determines the general composition of the generic PM in that classification mode. By its

23   nature then, exposure to airborne ambient PM constitutes an exposure to what is very clearly a

24   mixture of different particles of differing composition and to other gaseous co-pollutants that

25   coexist in that air-shed.

26   The epidemiology information reviewed in the 1996 PM AQCD and updated in this

27   document convincingly shows that a positive correlation exists between the levels of ambient PM

28   pollution and mortality/morbidity. However, this correlation is based mainly on a mass metric,

29   which is somewhat counter-intuitive considering the complexities in composition of PM and

30   given the perceptively low concentrations of most PM constituents, even when fractionated by

31   PM size. What has evolved since the 1996 PM AQCD is the advance in our understanding that

1   the linkages between PM exposure and health impacts is most strongly related to accumulation

2   mode particles, with combustion-derived PM typically being the most active of the source-based

3   contributors. It is also appreciated that discovery of a "magic bullet" regarding PM

4   physicochemical attributes is not likely to occur, and perhaps the sources from which the PM

5   derive may be the best linkage one can achieve.

6   Approaches to elucidating "causation" and "biological plausibility" have attempted to

7   integrate the wealth of epidemiological data with the growing body of toxicology to reveal

8   coherence among the findings to encourage the pursuit of sound hypotheses. Thus, while it is

9   often difficult to separate the physicochemical attributes of PM that may be of health significance

10   from the mechanisms by which individual factor(s) may function in the response, a number of

11   hypotheses have evolved espousing various PM characteristics as potentially significant

12   contributors to the observed health effects (reviewed by Dreher, 2000). Each of the attribute-

13   based hypotheses has a sufficient data base to merit consideration and further investigation.

14   As the science progresses, it is important that any hypothesis be critically evaluated in the context

15   of the problem, and that the hypothesis provide reasonable responses to at least the following

16   generic, yet pertinent questions (Chapman et al., 1997).

17   • Are there environmental sources that would lead to exposure to PM with the putative

18   constituent(s) or characteristic?

19   • Is there evidence of personal exposure involving PM with that attribute and effect?

20   • Does the putative attribute possess or contribute to a toxic potential?

21   • Is there evidence of an exposure-response relationship, especially at the low

22   concentrations found in the ambient environment?

23   • How well does the hypothesis generalize from one PM sample, exposure, or locale to

24   another?

25   To date, toxicologic studies on PM have provided important, albeit still limited, evidence

26   for specific PM attributes being primarily or essentially responsible for the cardiopulmonary

27   effects linked to ambient PM. In most cases, however, exposure concentrations in laboratory

28   studies have been inordinately high compared to the exposures at which epidemiologic studies

29   have found effects.   Reasons for this dosimetric discrepancy range from the limited numbers of

30   animals or human subjects that can be practically studied, the uncertainty and narrow range of

31   responsiveness of the study groups and especially the typically limited use of young, elderly,

1 unhealthy, or otherwise at-high-risk animals or humans, especially in light of poorly understood

2 risk factors. Thus, most of the toxicology data-base resides in the "Hazard-Identification"

3 compartment of the Risk Assessment paradigm. However, sufficient coherence in the

4 epidemiological and toxicological data has provided a level of "plausibility" to the observational

5 studies and have opened new avenues for investigation to link PM properties and constituents to

6 specific sources and to health outcomes. The primary PM properties thought to be related to

7 health effects are discussed below.

8

9.9.2 Specific Properties of Ambient PM Linked to Health Effects

9.9.2.1 Physical Properties

11   <u>Acid Aerosols</u>: There is relatively little new information on the effects of acid aerosols,

12 and the basic conclusions of the the 1996 PM AQCD remain unchanged. It previously was

13 concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects,

14 but asthmatics may experience small decrements in pulmonary function. Long-term exposures of

15 animals to acid aerosols, on the other hand, have been shown to alter airway morphology with

16 epithelial cell desquamation and an increase in secretory cells, but these changes have been

17 considered relatively minor. The conclusions about the acute health effects, however, are

18 supported by a recent study by Linn and colleagues (1997), in which healthy children (and

19 children with allergy or asthma) were exposed to sulfuric acid aerosol (100 μg/m^3) for 4 hours.

20 While there were no significant effects on symptoms or pulmonary function when the entire

21 group was analyzed, the allergy group did have significant acid-related increases in symptoms,

22 although the acid concentrations were distinctly higher than typical ambient concentrations.

23 These findings were consistent with those reported for adolescent asthmatics exposed to acid

24 aerosols in earlier studies reported in the 1996 PM AQCD.

25   Although pulmonary effects of acid aerosols have been the subject of extensive research,

26 the cardiovascular effects of acid aerosols have received little attention. One example, which

27 raises the issue is a study of acetic acid fumes where reflex mediated increases in blood pressure

28 were found in normal and spontaneously hypertensive rats (Zhang et al., 1997). Similarly, acidic

29 residual oil fly ash (ROFA) PM (which also contains a considerable amount of metal sulfates)

30 was found to alter ecocardiogram (ECG) patterns in the same strain of rats at high air

31 concentrations (Kodavanti et al., 2000). Thus, acidic components should not be entirely

1   dismissed as possible mediators of ambient PM health effects, since so little is known about

2   potential cardiovascular impacts or impacts in compromised subjects.

3

4   Ultrafine Particles (Size, Surface Area, Number): The physical attributes of PM - size,

5   surface area and number - are intimately interrelated. These properties influence lung deposition,

6   penetrance and persistence in lung tissues, and systemic transport, and, in several studies,

7   apparently the inherent toxicity of the particle itself. While a few epidemiological studies

8   (Wichmann et al., 2000) show correlations between health outcomes and ultrafine (<100 nm)

9   ambient PM, the bulk of the information regarding its toxic potential, and the role of surface

10   area, has derived from studies of surrogate insoluble particles, such as mineral oxides (e.g., TiO_2)

11   and carbon black (Oberdorster et al., 1994; Osier and Oberdorster, 1997; Li et al., 1997, 1999).

12   These studies have shown that on an equivalent mass exposure-dose metric, ultrafine PM can

13   induce more acute lung injury than fine PM. Similarly, surrogate PM with high surface areas

14   induced more toxicity than those of like composition, but having smaller surface areas (Lison

15   et al., 1997). On the other hand, studies have shown that composition also matters; for example

16   MgO ultrafines produce less injury than ZnO (Kuschner et al., 1997), as did sparked carbon

17   versus similarly generated metal oxides (Elder et al., 2000).

18   As with acid aerosols, studies of ultrafine particles have focused largely on effects in the

19   lung, but inhaled ultrafine particles may also have the potential to be distributed systemically and

20   have effects that are independent of lung effects. Recent epidemiological studies evaluating

21   blood viscosity as a biologic correlate of ultrafine exposures, have reported slight increases that

22   raise the prospect of potential cardiovascular implications (Wichmann et al., 2000).

23

24   Fine and Thoracic Coarse Particles: In contrast to ultrafine particles, the respective roles of

25   fine (<2.5 μm) and thoracic coarse (2.5-10 μm) particles in defining health outcomes have

26   garnered considerable research attention because they are the most frequently measured size-

27   fractions of ambient PM and for which most health effects data exist. The fine fraction

28   comprises most of the combustion-related constituents discussed below under chemicals and

29   most readily penetrates deeply into the respiratory tract - at least in terms of a mass metric dose.

30   Naturally, the fine fraction had greater surface area than the thoracic coarse fraction, but much

31   less surface area and particle number than the ultrafine fraction. To the extent that inhaled PM

1   may carry chemicals or reactive species on their surfaces, these smaller size fractions may have

2   an additional dimension to their toxicity (in terms of surface chemical bioavailablilty) that is not

3   found with coarse PM. For example, acute exposure to sulfate-coated carbon black was found to

4   impair alveolar macrophage phagocytosis and intrapulmonary bactericidal activity in mice (Jakab

5   et al., 1996; Clarke et al., 2000). On the other hand, coarse PM usually is of mineral (earthen) or

6   biologic (discussed below) origin and, thus, has a less complex bioavailable chemical matrix than

7   the finer PM mode. The relative toxicity of most earthen-derived PM has been observed to be

8   less than that of the finer combustion-derived or surrogate ultrafine particles. However, because

9   ambient coarse PM would tend to impact on the airways of humans, it is thought this fraction

10   may be adverse to those with airways sensitivities or disease (e.g., asthma).

11

12   **9.9.2.2 Chemical Properties**

13   <u>Inorganic Constituents</u>: The inorganic constituents of ambient PM comprise a number of

14   compounds and elements that derive from either natural or combustion sources. The earthen or

15   natural constituents of PM are typically silicates that contain surface and matrix bound metals

16   such as calcium, magnesium, aluminum, and iron. As noted above, most of these silicates do not

17   appear to contribute much toxicity to ambient PM, as considered in this document. Sulfate and

18   nitrate anions derived from combustion or photochemical processes usually complex with other

19   constituents in PM - often more water-soluble ammonium ions or organic acids, as well as

20   elemental cations, such as metals. The intrinsic, independent toxicities of sulfates (as per above)

21   and nitrates appear to be rather low, but they may influence the toxicity or bioavailability of other

22   PM components. Of the cations, metals represent a potential class of causal constituents for

23   PM-associated health effects that have received considerable attention (discussed in more detail

24   below). Sulfate, nitrate, ammonium, and metals make up a substantial part of the mass of

25   ambient PM, often with a silicate or carbonaceous (see below) core, layering, or matrix. The

26   majority of PM-associated metals in fine PM are derived from stationary or mobile combustion

27   sources whereas particle sulfate, nitrate and ammonium originate from secondary atmospheric

28   transformation reactions of involving SO_2, NO_x and biomass ammonia emissions. Organic PM

29   has both primary and secondary sources.

30

1   Metals: The 1996 PM AQCD relied on data from occupational exposures to initially

2   evaluate the potential toxicity of metals in PM air pollution. Since that time, *in vivo* and *in vitro*

3   studies using ROFA or soluble transition metals have contributed substantial new information on

4   the health effects of PM-associated soluble metals. The metals of most interest, notably the

5   transition metals of iron, vanadium, copper, nickel, chromium, cadmium, arsenic, are ubiquitous

6   constituents of PM-derived from anthropogenic fossil fuel emissions. Exposure seems to be

7   widespread with studies in autopsy specimens (1980's) showing dramatic increases in the content

8   of the first row transition metals in lung tissues of Mexico City residents since the 1950's

9   consistent with industrialization and pollution (Fortoul et al., 1996). Similar studies in North

10   America show metals in the lung tissues of urban dwellers. Although there remain uncertainties

11   about the differential effects of one transition metal versus another, water-soluble or bioavailable

12   metals leached from ROFA or bulk ambient PM cause a variety of biological effects. Many

13   studies show that the action of instilled ROFA and constituent metals are pro-inflammatory

14   (cells, mediators, and molecular signaling processes - *in vivo* and *in vitro*), and recently, they

15   have been shown to induce cardiac arrhythmias in animal models (both healthy and diseased).

16   In studies in which various ambient and emission source PM were instilled into rats, the soluble

17   metal content appeared to be the primary determinant of lung injury (Costa and Dreher, 1999).

18   However, these and the related findings on metal toxicity generally have derived from relatively

19   high dose instillation or inhalation exposures, lending them to criticism as to their relevancy for

20   ambient PM that is low in metal content.

21   Nevertheless, a series of studies associated with the closing of a metal smelter in Utah

22   Valley, where ambient PM extracts (containing metals and other soluble constituents) were

23   instilled into the lungs of humans (Ghio and Devlin, 2001) and animals (Dye et al., 2001), as

24   well as tested in vitro (Frampton et al., 1999), showed remarkable coherence with

25   epidemiological studies of hospitalization and mortality (Pope, 1989; Pope et al., 1999b) in the

26   same area and at the same times of the PM samples used in the laboratory studies. The response

27   patterns in each study paralleled the metal content. Furthermore, recent application of novel

28   statistical approaches to the study of source-associated constituents (often metals are the

29   elemental markers) have shown promise in linking sources with their associated emission

30   profiles (including metals) to health outcomes in both humans (Laden et al., 2000) and animals

1   (Clarke et al., 2000). Thus, while metals appear to be one component involved in PM associated

2   health effects, the full story is incomplete.

3

4   Organic Constituents: Published research on the acute effects of PM-associated organic

5   carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles

6   (DEP). Like metals, organics are common constituents of combustion-generated PM and are

7   found in ambient PM samples over a wide geographical range. Organic carbon constituents

8   comprise a substantial portion of the mass of ambient PM (10 to 60% of the total dry mass

9   [Turpin, 1999]). Although the organic fraction of PM is a poorly characterized heterogeneous

10   mixture of a widely varying number of different compounds, strategies have been proposed for

11   examining the health effects of potentially important organic constituents (Turpin, 1999).

12   In contrast, the mutagenic effects of ambient PM and evidence of DNA-adducts have had more

13   extensive study and have been linked to specific organic fractions (Binkova et al., 1999; Chorąży

14   et al., 1994; Izzotti et al., 1996). The extent to which organic constituents of ambient PM

15   contribute to adverse health effects identified by current epidemiology studies is not known.

16   Nevertheless, organic constituents remain of concern regarding PM health effects due in large

17   part to the contribution of DEP to the fine PM fraction and the health effects associated with

18   exposure to these particles.

19

20   Diesel Exhaust Particles (DEP): There is growing toxicological evidence that DEP

21   exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has

22   been linked to eosinophil degranulation and induction of cytokine production suggesting that the

23   organic constituents of DEP are responsible for the immune effects. It is known that the

24   adjuvant-like activity of DEP is not unique, and that certain metals have analogous adjuvant

25   effects (Lambert et al., 2000). It is important to compare the immune effects of other source-

26   specific emissions, as well as concentrated ambient PM, to DEP to determine the extent to which

27   exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and

28   asthma. Other types of noncancer and carcinogenic (especially lung cancer) effects are of

29   concern with regard to DEP exposures, as discussed in a separate EPA Health Assessment

30   Document for Diesel Exhaust (U.S. Environmental Protection Agency, 2002).

31

1   <u>Biogenic Constituents</u>: Recent studies support the conclusion of the 1996 PM AQCD that

2   bioaerosols, at the concentrations present in the ambient environment, are unlikely to account for

3   the health effects of ambient PM. Dose-response inhalation studies in healthy volunteers

4   exposed to 0.55 and 50 μg endotoxin showed the threshold for pulmonary and systemic effects

5   for endotoxin to be between 0.5 and 5.0 μg (Michel et al., 1997). Urban ambient air PM contains

6   variable amounts of endotoxin, but the levels typically are several orders of magnitude less. The

7   *in vitro* toxicological studies that have shown endotoxin associated with ambient PM to be pro-

8   inflammatory, inducing cytokine expression in human and rat alveolar macrophages, appear to

9   relate to the endotoxin dose to cell ratio (Becker et al., 1996; Dong et al., 1996). However,

10   endotoxin content does appear to vary by size-mode. Monn and Becker (1999) demonstrated

11   cytokine induction by human monocytes, characteristic of endotoxin activity, in the coarse size

12   fraction of outdoor PM, but not in the fine fraction. Interestingly, while studies in animals

13   models also require more endotoxin than typically found in ambient PM to induce inflammation,

14   recent studies suggest endotoxin may have a priming effect on PM-induced inflammatory

15   processes (Imrich et al., 1999). Thus, the role of biogenic material like endotoxin may have a

16   subtle role that is poorly understood.

17

18   **9.9.2.3 Summary**

19   Toxicological studies have provided considerable supportive evidence that certain

20   physicochemical particle attributes can provide elements of "causality" to observed health effects

21   of ambient PM. A primary causative attribute may not exist but rather many attributes may

22   contribute to a complex mechanism driven by the nature of a given PM and its contributing

23   sources. The multiple interactions that may occur in eliciting a response in a host may make the

24   identification of any single causal component difficult and may account for the fact that mass as

25   the most basic metric shows the relationships to health outcomes that it does.

26

27   **9.9.3 Chemical Components and Source Categories Associated with Health**
28   **   Effects in Epidemiologic Studies**

29   Epidemiologic studies using either individual chemical species or classes or using source

30   category factors (SCF) derived from factor analysis have identified a variety of species whose

1 ambient concentrations are statistically associated with either total mortality or more specific

2 mortality groupings.

3

4 **9.9.3.1 Individual Chemical Species**

5   Table 9-10 lists the various gaseous co-pollutants, size fractions, chemical element or ions,

6 and organic fractions that have been found to be associated with mortality in regressions using

7 one pollutant species at a time.

8

9

TABLE 9-10. CHEMICAL SPECIES ASSOCIATED WITH MORTALITY IN EPIDEMIOLOGIC STUDIES

Co-Pollutants	PM Size Fractions	Ions/Elements	Carbon/Organic Fractions
CO	TSP	$SO_4^=$	TC (Total Carbon)
NO_2	PM_{10}	NO_3^-	EC (elemental Carbon)
SO_2	$PM_{2.5}$	Ni	BC (Black Carbon)
O_3	$PM_{10-2.5}$	Pb	COH (Coefficient of Haze)
	$PM_{0.1}$		OC Organic Carbon)
	number		CX (Cyclohexene-extractable Carbon)

1 **9.9.3.2 Source Category Factors**

2   There are also three studies in which factor analysis has been used to identify several

3 specific source category factors. In two cases (Laden et al., 2000 and Tsai et al., 2000), the

4 source category factors (SCF) were then used in a multiple regression, the nonsignificant factors

5 were eliminated, and the multiple regression was rerun with only the significant factors. In the

6 third case (Mar et al., 2000), relative risk values are reported for regression with SCF one at a

7 time but the paper states that "Regression analysis with all of the factors included in a

8 multi-source model produced similar results." The similar results in single and multiple

9 regressions and the low correlation between SCF indicates that there is low potential for

10 confounding among the various SCFs.

1   Source categories that have been found to be significantly associated ($p < 0.05$) with total,

2 cardiovascular, or cardiovascular plus respiratory mortality in one or more cities are shown in

3 Table 9-11. A source category associated with motor vehicles was found in all four studies. The

4 epidemiological studies do not provide sufficient information to determine whether the causal

5 factor is one or both of the gaseous co-pollutants (CO and NO_2); soot particles from cars

6 (indexed by BS, COH, or EC); organic PM from vehicles, transition metals emitted by vehicle

7 (Mn, Fe, Zn); or other particles generated or resuspended by vehicular traffic.

8

9

TABLE 9-11. SOURCE CATEGORIES ASSOCIATED WITH MORTALITY IN EPIDEMIOLOGIC STUDIES

Source Category	Tracers
Tsai et al. (2000)	
Motor vehicles	CO
Fuel Oil Combustion	Ni, V
Sulfate	S
Industrial	Zn, Cd
Laden et al. (2000)	
Motor Vehicles	Pb
Coal Burning (sulfate)	Se, (S)
Mar et al. (2000)	
Motor Vehicles	CO, NO_2; EC, OC; Mn, Fe, Zn, Pb
Vegetative Burning	OC, non-soil K
Sulfate	S
Özkaynak et al. (1996)	
Motor vehicles	CO, COH, NO_2

1   The three studies that investigated multiple source categories also found a sulfate factor.

2 The factor reported by Laden et al. (2000) as "coal burning" contains high loadings of both

3 selenium and sulfur and could also have been called "regional sulfate". Mar et al. (2000) refer to

1 the factor with high sulfate specifically as "regional sulfate". They were able to make this

2 connection because they also had a factor with a high loading of SO_2 which they called a "local

3 SO_2" factor. The regression with the chemical species S (assumed due to sulfate) was not

4 significant, but the regression with the regional sulfate factor was significant. This may be

5 because the factor analysis will tend to remove other more localized sulfate sources such as

6 $CaSO_4$ and Na_2SO_4, leaving only acid sulfates ($[NH_4]_2SO_4$, NH_4HSO_4, and H_2SO_4) for a regional

7 sulfate factor. (In Phoenix, there was a modest loading of S in the soil factor.) Therefore, all

8 three sulfate factors should be considered as regional sulfate.

9   The studies of specific chemical components and source categories are especially important

10 because they indicate the association of health effects with the three major components of PM

11 mass: sulfate, nitrate, and organic PM. Examination of $PM_{2.5}$ and nitrate effects, alone and in

12 multiple regressions, indicates that $PM_{2.5}$ and nitrate were not confounded by NO_2, CO or O_3 in

13 Santa Clara, CA (Fairley, 1999). Examination of the lag structure from the Phoenix study reveals

14 that neither the regional sulfate factor nor the vegetative burning factor was confounded by NO_2,

15 CO, SO_2, or O_3. The epidemiologic results suggest the need for toxicologic studies of the sulfate,

16 nitrate, and organic components of PM, including studies with compromised or susceptible

17 subjects.

18   All of the studies that investigated multiple source categories found a soil or crustal source

19 that was negatively associated with mortality. This suggests that the components of natural soil

20 may have minimal toxicity unless contaminated by anthropogenic sources, such transition metals

21 or polyaromatic hydrocarbons. In any event, the epidemiologic associations suggest additional

22 PM components that should be investigated in toxicologic studies.

23

24

25 ## 9.10 SUSCEPTIBLE SUBPOPULATIONS

26   *What subpopulations are at increased risk of adverse health outcomes from particulate*

27 *matter?*

28

29

9.10.1 Introduction

The 1996 PM AQCD identified several population groups potentially being at increased risk for experiencing health impacts of ambient PM exposure. Elderly individuals (>65 years) were most clearly identified, along with those having preexisting cardiovascular or respiratory disease conditions. Smokers and ex-smokers likely comprise a large percentage of individuals with cardiovascular and respiratory disease, e.g., chronic obstructive pulmonary disease (COPD). Individuals with asthma, especially children, also were identified as a potential susceptible population group. The studies appearing since the 1996 PM AQCD provide additional evidence to substantiate the above named groups as likely being at increased risk for ambient PM-related morbidity or mortality effects. There is even evidence, though quite limited at this time, of prenatal effects on cardiac development and potential mortality impacts on infants in the first two years of life.

While the identification of susceptible population groups is a critical element of the risk paradigm, characterizing risk factors that underlie susceptibility and that may be common to multiple groups would better substantiate risk estimates and provide better predictability to PM responsiveness. Information relating to these factors, as gleaned from recent epidemiology and toxicology studies, suggests contributing host attributes that may be useful in gaining perspective on their relative public health impact.

9.10.2 Preexisting Disease as a Risk Factor for Particulate Matter Health Effects

The information reviewed in the 1996 PM AQCD is now augmented by numerous new studies which substantiate the finding that preexisting disease conditions represents an important risk factor for ambient PM health effects. Cardiovascular and respiratory diseases continue to appear to be of greatest concern in relation to increasing risk for PM mortality and morbidity. Indeed, the fact that these disease 'entities' often involve both organ systems, albeit to varying degrees, might argue for their compilation under a broader classification of 'cardiopulmonary' disease. Nevertheless, as they are diagnosed and reported separately, Table 9-12 shows the 1996 numbers of U.S. cases reported for COPD, asthma, heart disease, and hypertension.

**TABLE 9-12. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND
BY GEOGRAPHIC REGION, 1996**

(reported as incidence per thousand population and as number of cases in thousands)

Chronic Condition/Disease	Age					Regional			
	All Ages	Under 45	45-64	Over 65	Over 75	NE	MW	S	W
COPD[*]									
Incidence/1,000 persons	60.4	50.6	72.3	95.9	99.9	57.8	67.6	59.4	56.6
No. cases × 1,000	15,971	9,081	3,843	3,047	1,334				
Asthma									
Incidence/1,000 persons	55.2	58.9	48.6	45.5	48.0	61.8	56.6	51.8	52.9
No. cases × 1,000	14,596	10,570	2,581	1,445	641				
Heart Disease									
Incidence/1,000 persons	78.2	33.1	116.4	268.7	310.7	88.5	78.0	77.0	70.4
No. cases × 1,000	20,653	5,934	6,184	8,535	4,151				
HD-ischemic									
Incidence/1,000 persons	29	2.5	51.6	140.9	154.6	28.9	30.0	30.7	25.0
No. cases × 1,000	7,672	453	2,743	4,476	2,065				
HD-rhythmic									
Incidence/1,000 persons	33	24.3	40.7	69.1	73.1	40.2	34.0	28.1	32.9
No. cases × 1,000	8,716	4,358	2,164	2,195	977				
Hypertension									
Incidence/1,000 persons	107.1	30.1	214.1	363.5	373.8	109.3	108.2	113.5	93.7
No. cases × 1,000	28,314	5,391	11,376	11,547	4,994				

[*]Total chronic bronchitis and emphysema.

Source: Adams et al. (1999).

9.10.2.3 Ambient PM Exacerbation of Respiratory Disease Conditions

Many time-series studies have shown that pre-existent chronic lung diseases as a group (but especially chronic obstructive pulmonary disease - COPD) constitutes a risk factor for mortality with PM exposure. Studies with humans that might reveal more specific data have been limited both ethically, as well as by the absence of good biomarkers of response (such as ECG's serve cardiac disease). Measures of blood-gas saturation and lung function appear not to be sufficiently revealing or sensitive to mild physiologic changes in those with moderate disease conditions who might be amenable to lab study. In the field, assessing the degree of underlying disease and how that relates to responsiveness of these biomarkers is unclear. However, subjects with COPD and asthma have been studied with inert aerosols for the purpose of assessing distribution of PM within the lung, and it is now quite clear that airways disease leads to very heterogeneous distribution of PM deposited within the lung. Studies have shown up to 10-fold higher than normal deposition at airway bifurcations, thus creating "hot-spots" that may well have biologic implications, especially if the individual already has diminished function or other debility due to the underlying disease, even CVD. Thus the dosimetry of PM within the lung must be considered an important element of the susceptibility paradigm with most any cardiopulmonary disease condition.

There are several reports of associations between short-term fluctuations in ambient PM and day to day frequency of respiratory illness. In most cases, notably in children and young people, exacerbation of preexisting respiratory illness and related symptoms has been assessed rather than *de novo* acute respiratory infections, with asthma apparently an additional risk factor. The use of inhalers has also been shown to increase in many young asthmatics in response to air pollution, with PM often noted as the primary correlate, and as a result school absenteeism increases, again especially in asthmatic children. Interestingly, acute respiratory infections in the elderly with cardiopulmonary disease appears to result in complications of underlying cardiac disorders when PM exposure is involved (Zanobetti et al., 2000), and likewise is linked to subsequent hospitalization. Animal studies with surrogate PM, however, show varied impact on the induction of infection, but in general can alter lung phagocyte functions, which might worsen the condition. Thus, while there appears to a strong likelihood that infections may be worsened by exposure to PM, general statements regarding interaction of PM with response to infectious

1 agents are difficult given the unique attributes of various infectious agents and the immune status
2 of the host.

3   The underlying biology of lung diseases might also lead to heightened sensitivity to PM
4 (apart from the dose issue noted above), but this attribute of disease remains hypothetical in the
5 context of PM. The functional linkages with the cardiac system for maintenance of adequate gas
6 exchange and fluid balance notwithstanding, the role of inflammation in the diseased respiratory
7 tract (airways and alveoli) could play a key role. Studies in animals genetically or exogenously
8 altered to induce inflammation are sometimes intrinsically more responsive to surrogate or
9 concentrated ambient PM. While a PM-induced response may on the one hand be cumulative
10 with the underlying injury or condition, the responses may, on the other hand, be magnified by
11 any number of mechanisms that are poorly understood. There is sufficient basic biological data
12 to hypothesize that the exudated fluids in the airspaces may either interact differently with
13 deposited PM (e.g., to generate oxidants - Costa and Dreher, 1999; Ghio et al., 2001) to augment
14 injury, or predispose the lung (e.g., sensitize receptors - Undem and Carr, 2002) to enhance the
15 response to a stereotypic PM stimulus through otherwise normal pathways. Less appreciated is
16 the loss of reserve - functional or biochemical - where the susceptible individual is incapable of
17 sufficient compensation (e.g., antioxidant responses - Kodavanti et al., 2000). Any of these or
18 related mechanisms may contribute to "susceptibility" and may indeed be a common factor that
19 can be attributable to other susceptible groups. Understanding these will ultimately aid in
20 addressing true risk of susceptible groups to PM.

21   Again, even a small percentage reduction in PM health impacts on respiratory-related
22 diseases could calculate out to a large number of avoided cases. In 1997, there were 3,475,000
23 U.S. hospital discharges for respiratory diseases: 38% for pneumonia, 14% for asthma, 13% for
24 chronic bronchitis, 8% for acute bronchitis, and the remainder not specified (Lawrence and Hall,
25 1999). Of the 195,943 deaths recorded as caused by respiratory diseases, 44% resulted from
26 acute infections, 10% from emphysema and bronchitis, 2.8% from asthma, and 42% from
27 unspecified COPD (Hoyert et al., 1999).

28

29 **9.10.2.4 Ambient PM Exacerbation of Cardiovascular Disease Conditions**
30   Exacerbation of cardiovascular (CVD) has been associated epidemiologically, not only
31 with ambient PM, but also with other combustion-related ambient pollutants such as CO. Thus,

1   while leaving little doubt that ambient PM exposures importantly affect CVD mortality and

2   morbidity, the quantitation of the proportion of risk for such exacerbation specifically attributable

3   to ambient PM exposure is difficult. Recent studies (e.g., concentrated ambient particle studies

4   [CAPS]) have demonstrated cardiovascular effects in response to ambient particle exposures, and

5   studies utilizing animals and other approaches also have produced results suggesting plausible

6   mechanisms leading to cardiovascular effects. However, much remains to be resolved with

7   regard to delineation of dose-response relationships for the induction and extrapolation of such

8   effects to estimate appropriate and effective human equivalent PM (or specific constituent/s)

9   exposures.

10   The recent appreciation for underlying cardiovascular dysfunction as a risk factor for PM

11   health effects derives from a growing and diverse body of literature. While many time-series

12   studies have revealed stronger associations between PM exposures and mortality when a

13   subpopulation was segregated for pre-existent cardiac disease, no direct and plausible evidence

14   had been available. However, recent panel studies of human subjects with CVD (Peters et al.,

15   2000) have shown correlations between air pollution levels, notably PM, and intervention

16   discharge frequency of implanted cardiac defribrillators. Analogously, Pope and colleagues

17   (2001) have noted altered autonomic control of cardiac electrocardiograms (in terms of Heart

18   Rate Variability) over a wide age- range of ostensibly healthy subjects when they were

19   introduced into a room with active smokers. Evidence of vascular narrowing with exposure to

20   concentrated ambient PM (CAPS) has likewise been reported suggesting parallel cardiovascular

21   responses (Brook et al., 2002). Collectively, these and previous studies that have shown ambient

22   PM-induced alterations in cardiac physiology (Pope et al, 1999a,b; Liao et al., 1999; Peters et al.,

23   1999a; Gold et al., 2000) in human subjects, complemented with animal studies (Godleski et al.,

24   1996; Watkinson et al., 1998, 2001; Kodavanti et al., 2000), reinforce the notion of significant

25   cardiac responses to PM. Moreover, indications of changes in plasma viscosity (Peters et al.,

26   1997a) and other factors involved in clotting function (Ghio et al., 2000) provide a plausible

27   cascade of events that could culminate in a sudden cardiac events in some individuals.

28   The HEI report on an epidemiologic study in Montreal, Canada by Goldberg et al. (2000),

29   provides interesting new information regarding types of medical conditions potentially

30   predisposing susceptible individuals to increased risk for PM-associated mortality. It is

31   specifically suggestive that other diseases involving cardiovascular complications could also

1   contribute to PM risk. First, the immediate causes of death, as listed on death certificates, were

2   evaluated in relation to various ambient PM indices (TSP, PM_{10} estimated $PM_{2.5}$, COH, sulfates,

3   and extinction coefficients) lagged for 0 to 4 days. Significant associations were seen between

4   each of the PM measures and total nonaccidental deaths, respiratory diseases, and diabetes, with

5   an approximate 2% increase in excess nonaccidental mortality being observed per 9.5 $\mu g/m^3$

6   interquartile increase in 3-day mean estimated $PM_{2.5}$ exposure. When underlying clinical

7   conditions identified in the decedents' medical records were then evaluated in relation to ambient

8   PM measures, all three measures (COH, sulfate, and estimated $PM_{2.5}$) were associated with acute

9   lower respiratory disease, congestive heart failure, and any cardiovascular disease. Predicted

10   $PM_{2.5}$ and COH also were reported to be associated with cancer, chronic coronary artery disease,

11   and any coronary artery disease, whereas sulfate was associated with acute and chronic upper

12   respiratory disease. None of the three PM measures were related to airways disease, acute

13   coronary artery disease, or hypertension. These results both tend to confirm previous findings

14   identifying those with preexisting cardiopulmonary diseases as being at increased risk for

15   ambient PM effects and implicate another possible risk factor, diabetes (which involves

16   cardiovascular complications as it progresses), as a potential susceptibility condition putting

17   individuals at increased risk for ambient PM effects. Zanobetti and Schwartz (2001) have

18   likewise found, perhaps more directly, that those with diabetes are at increased risk, presumably

19   related to the cardiac and vascular complications associated with this disease.

20   To the extent that the observed associations between ambient PM and heart disease

21   exacerbation are causal and specific, the impact on public health could be dramatic. In 1997,

22   there were about 4,188,000 U.S. hospital discharges with heart disease as the first-listed

23   diagnosis (Lawrence and Hall, 1999). Among these, about 2,090,000 (50%) were for ischemic

24   heart disease, 756,000 (18%) for myocardial infarction or heart attack (a subcategory of ischemic

25   heart disease), 957,000 (23%) for congestive heart failure, and 635,000 (15%) for cardiac

26   dysrhythmias. Also, there were 726,974 deaths from heart disease (Hoyert et al., 1999). Thus,

27   even a small percentage reduction in PM-associated admissions or deaths from heart disease

28   would predict a large number of avoided cases.

29

30

9.10.3 Age-Related At-Risk Population Groups: The Elderly and Children

The very young and the very old apparently constitute another group especially affected by PM air pollution. As noted above, a major factor in increased susceptibility to air pollution is the presence of a preexisting illness, as discussed by Zanobetti and Schwartz (2000).

The impact of PM pollution is well-documented in time-series studies with mortality risk in studies where age is a factor in the analysis, risk increases above the age of 45 and continues to increase significantly throughout the remainder of life. Cardiopulmonary diseases more common to the elderly play into the risk within older age groups, but panel studies of morbidity focusing on generally healthy people in retirement homes or elderly volunteers exposed to concentrated ambient PM in chambers show subtle alterations of autonomic control of cardiac function (i.e., slight depression of heart rate variability) and blood factors concordant with a putative response to ambient PM levels. Though small, these changes are considered clinically significant based on studies of risk in cardiac patients and general population studies of cardiac disease progression. Moreover, these changes are in contrast to the lack of similar physiologic changes in healthy young people. Over the long term, innate differences in metabolism or other mechanisms may impact the likelihood of chronic outcomes, e.g., COPD or lung cancer. To what extent progression occurs with repeated PM exposures and how much disease or other risk factors add to or complicate the magnitude of response remains uncertain.

Although infection as a risk factor for PM has already been discussed, it is important to emphasize that there are clear age differences in both the incidence and type of infections across age groups. Young children have the highest rates of respiratory illnesses related to infection (notably respiratory synctial virus), while adults are affected by other infectious agents such as influenza that may also lend susceptibility to PM. Data to fully address the importance of these differences is incomplete. The distribution of infectious lung diseases in the U.S. in 1996, summarized in the Table 9-13, provides a good overview of the diversity of this category of preexisting lung disease.

In addition to their higher incidences of preexisting respiratory conditions, several other factors may render children and infants more susceptible to PM exposures, including more time spent outdoors, greater activity levels and ventilation, higher doses per body weight and lung surface area, and the potential for irreversible effects on the developing lung. For example, PM doses on a per kilogram body weight basis are much higher for children than for adults as is

**TABLE 9-13. NUMBER OF ACUTE RESPIRATORY CONDITIONS PER
100 PERSONS PER YEAR, BY AGE: UNITED STATES, 1996**

Type of Acute Condition	All Ages	Under 5 Years	5-17 Years	18-24 Years	25-44 Years	45 Years and Over		
						Total	45-64 Years	65 Years and Over
Respiratory Conditions	78.9	129.4	101.5	86.0	76.9	53.3	55.9	49.0
Common Cold	23.6	48.6	33.8	23.8	18.7	16.1	16.4	15.7
Other Acute Upper Respiratory Infections	11.3	13.1	15.0	16.1	11.6	7.0	7.5	6.1
Influenza	36.0	53.7	44.3	40.5	38.1	23.3	26.1	18.6
Acute Bronchitis	4.6	*7.2	4.3	*3.9	5.1	3.8	3.5	*4.4
Pneumonia	1.8	*3.9	*1.7	*1.4	*1.3	*2.0	*0.9	*3.8
Other Respiratory Conditions	1.7	*2.9	*2.4	*0.4	*2.0	*1.1	*1.5	*0.5

Source: Adams et al. (1999).

1   displayed graphically in Figure 9-23. The amount of air inhaled per kilogram body weight

2   decreases dramatically with increasing age, due in part to ventilation differences (in cubic meters

3   per kilogram a day) of a 10-year-old being roughly twice that of a 30-year-old person, even

4   without the consideration of activity level. Child-adult dosage disparities are even greater when

5   viewed on a per lung surface-area basis.

6   As to potential lung developmental impacts of PM, there exist both experimental and

7   epidemiologic data, which although limited, suggest that the early post-neonatal period of lung

8   development is a time of high susceptibility for lung damage by environmental toxicants.

9   In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants

10 has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi,

11 2000); and acute injury to the lung during early postnatal development may impair normal repair

12 processes, such as down-regulation of cellular proliferation (Smiley-Jewel et al., 2000, Fanucchi

13 et al., 2000). These results in animals appear concordant with recent findings for young children

14 growing in the Los Angeles area where both oxidants and high PM prevail (Gauderman et al.,

15 2000).

16   These and other types of health effects in children are emerging as potentially more

17 important than appreciated in the 1996 PM AQCD. Unfortunately, relatively little is known
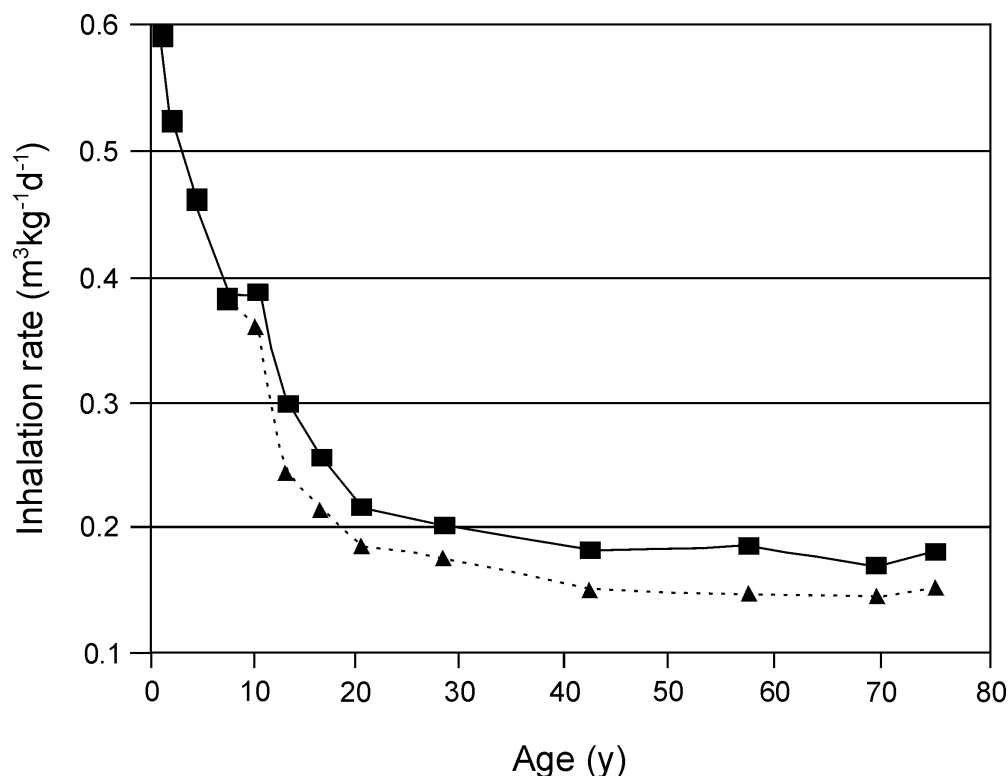
Figure 9-23. Inhalation rates on a per body-weight basis for males (■) and females (▲) by age (Layton, 1993).

1   about the relationship of PM to these and other serious health endpoints (low birth weight,

2   preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in

3   older children). The recent report by Ritz et al. (2002) linking CO exposures of mothers in

4   Los Angeles with fetal cardiac defects raises concerns for PM, which was inconclusively linked

5   in the study. Similarly, little is yet known about the involvement of PM exposure in the

6   progression from less serious childhood conditions, such as asthma and respiratory symptoms, to

7   more serious disease endpoints later in life. Thus, the loss of productive life-years that add to the

8   costs to society may be more than just those indexed by PM-related mortality and/or hospital

9   admissions/visits.

10   In summary, host variability may come to be the most important factor in determining the

11   response profile of any population exposed to PM. Studies to date suggest that certain

12   subpopulations are indeed more acutely responsive to PM, perhaps due to differences in lung

1 deposition (either in terms of dose and/or intrapulmonary distribution) or other biologic aspects

2 of the cardiopulmonary system or disease thereof. The role of innate attributes of risk grounded

3 in one's genetic code is largely unknown but potentially of great importance. Animal models

4 have been used to show clear differences in response to PM and other pollutants, and the critical

5 involvement of varied genes in the induction of asthma, emphysema, and many other ailments is

6 widely accepted, but poorly understood.

7

8

9.11   MECHANISMS OF INJURY

10   *What are the mechanisms by which acute exposure to PM causes adverse health effects?*

11

12   Numerous epidemiologic studies have shown statistically significant associations between

13 ambient PM levels and a variety of human health endpoints, including mortality, hospital

14 admissions, emergency department visits, respiratory illness, and symptoms measured in

15 community surveys. These associations have been observed with both short and long-term PM

16 exposure. There was little information available in the 1996 PM AQCD to provide biologically

17 plausible mechanisms to support the epidemiologic observations. However, in the intervening

18 years significant progress has been made in identifying pathophysiological effects in humans and

19 animals exposed to various PM that can provide insight into the mechanisms by which PM may

20 exert its effects. Potential mechanisms include neural mechanisms affecting the autonomic

21 nervous system (ANS) via direct pulmonary reflexes or through pulmonary inflammatory

22 processes, direct effects of PM or its components on ion channel function in myocardial cells,

23 ischemic responses of the myocardium, or systemic responses including inflammation that can

24 trigger endothelial cell dysfunction, and thrombosis via alterations in the coagulation cascade.

25 The interactions between these pathways which may lead to sudden cardiac death is shown in the

26 Figure 9-24. However, it must be noted that PM is a complex mixture of many different

27 components and it is possible that different components may stimulate different mechanistic

28 pathways. Thus exposure to PM may result in one or more pathways being activated, depending

29 on the chemical and physical makeup of the PM.

30
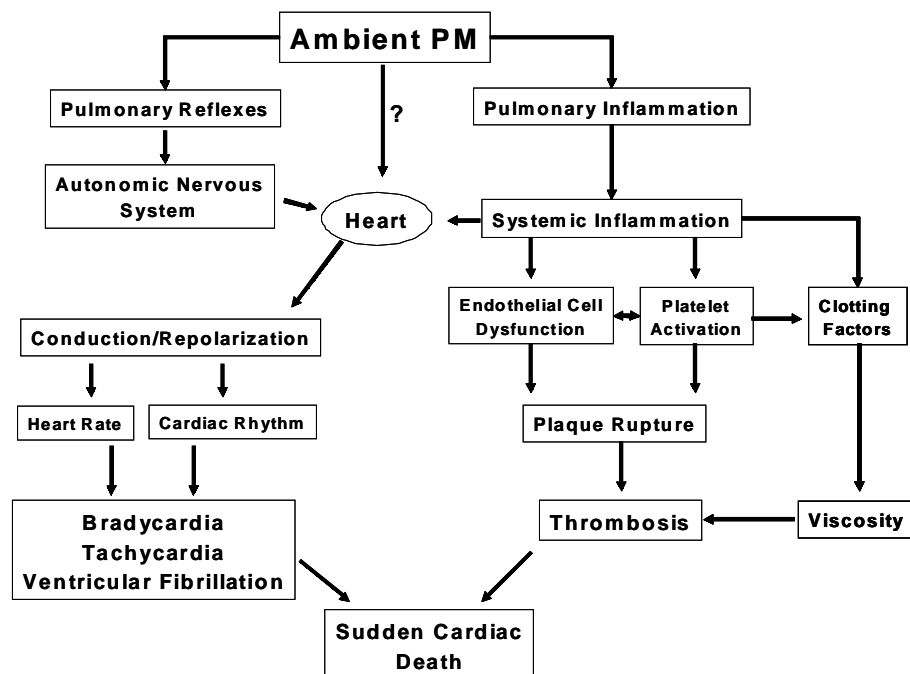
Figure 9-24. **Schematic representation of potential pathophysiological pathways and mechanisms by which ambient PM may increase risk of cardiovascular morbidity and/or mortality.**

1   There is now ample evidence that inhaled particles can affect the heart through the ANS.

2   Direct input from the lungs to the ANS via pulmonary afferent fibers can affect both heart rate

3   (HR) and heart rate variability (HRV). The heart is under the constant influence of both

4   sympathetic and parasympathetic innervation from the ANS; and monitoring changes in HR and

5   HRV can provide insight into the balance between those two ANS subdivisions. During recent

6   decades a large clinical database has developed describing a significant relationship between

7   autonomic dysfunction and sudden cardiac death. One measure of this dysfunction, low HRV,

8   has been implicated as a predictor of increased cardiovascular morbidity and mortality. Several

9   independent epidemiologic panel studies of elderly volunteers (some having cardiovascular or

10   pulmonary disease) have reported associations between PM concentrations and various measures

11   of HR and HRV. Although there are some differences among the studies, in general they report

12   an association between PM levels and a reduction in the standard deviation of normal to normal

13   beat intervals (SDNN), a time-domain variable of which the reduction was associated in the

1   Framingham Heart Study with a higher risk of death. Some studies also reported an association

2   between PM and decreased HRV in the high frequency (HF) range, which is a reflection of

3   parasympathetic modulation of the heart. Other studies have reported a positive association

4   between PM and HR; elevated HR has been associated with hypertension, coronary heart disease,

5   and death. Thus taken as a whole, evidence from panel studies indicates that PM can directly

6   affect the ANS in such as way as to alter heart rate and heart rate variability. However, it should

7   be noted that lowered HRV has primarily been used as a predictor of subsequent increased

8   mortality and morbidity. It is not clear whether a single reversible acute change in HRV places a

9   person more at risk for an immediate adverse cardiac event. Whether changes in HRV associated

10   with exposure to PM represent an independent risk or is just a marker of exposure is not yet

11   known.

12   PM as also been shown to induce changes in conductance and repolarization of the heart as

13   well. Repolarization duration and morphology may reflect subtle changes in myocardial

14   substrate and vulnerability governed by changes in ion channel function. There is considerable

15   evidence linking changes in T wave morphology, QT and T wave variability, T wave Alternans,

16   and changes in ST segment height, to the risk of sudden death. In some studies, rodent models of

17   susceptibility (monocrotaline injected, spontaneously hypertensive) exposed to ROFA showed

18   exacerbated ST segment depression, a factor reflecting T wave morphology during repolarization

19   and which as been useful in diagnosing patients with ischemic heart disease. Healthy dogs

20   exposed to CAPS also showed changes in ST segment elevation; this was exacerbated in dogs

21   with coronary artery occlusion.

22   While PM-induced changes in HRV and HR, as well as changes associated with

23   repolarization and conductance, have the potential to progress to malignant arrhythmias, there is

24   now evidence from both human and animal studies that PM exposure may be linked with severe

25   events directly associated with sudden cardiac death. A recent epidemiology study of patients

26   with implanted cardiac defibrillators reported associations between PM and increased

27   defibrillator discharges. Presumably, some of these patients would have suffered a fatal event

28   had they not had an implanted defibrillator. A second study reported that the risk for myocardial

29   infarction (MI) onset increased in association with PM levels in the 2 hours preceding the MI.

30   PM exposure has also been linked with malignant arrhythmia in some toxicology studies.

31   Healthy rodents exposed to ROFA demonstrated an increase in serious arrhythmic events,

1   including bradycardia. Rats treated with monocrotaline had significantly exacerbated

2   arrhythmias, and some animals even died within 24 hours following exposure. Older rats,

3   exposed to both ROFA and PM collected from Ottowa, also experienced increased arrhythmias.

4   Dogs exposed to CAPS experienced a slight bradycardia following exposure. Some of these

5   studies involved instillation of a specific PM component (ROFA) at high concentrations, making

6   it uncertain that these observations would hold true using ambient PM at more realistic

7   concentrations. Nevertheless, at least one study used ambient particles collected from Ottowa,

8   and other studies exposed animals by inhalation to CAPS. Taken as a whole, these studies

9   provide convincing evidence that exposure of animals to high levels of PM can affect

10   conductance and repolarization, potentially leading to fatal arrhythmias. However, it remains to

11   be seen if these mechanisms, that can potentially explain acute mortality associated with PM

12   exposure, operate at the lower concentrations of ambient PM to which most people are exposed.

13   Particulate matter could potentially affect the ANS by direct interaction with nerve ending

14   in the lung, or indirectly through the production of inflammatory mediators. Numerous studies

15   have documented that exposure of rodents to ROFA results in substantial lung inflammation and

16   injury. However, due to the levels of ROFA used in many of these studies and the fact that

17   ROFA only makes up a small portion of most airsheds, studies with ambient air particles may be

18   more relevant. There are several studies in which humans, dogs, or rodents have been exposed to

19   CAPS and mild pulmonary inflammation observed. Other studies have shown similar effects

20   when ambient PM collected on filters was used. However, the level of inflammation was quite

21   low in most of these studies, certainly lower than reported in humans or animals exposed to

22   ozone, and it is not yet clear whether lung inflammation plays a role in PM-induced changes in

23   the ANS.

24   In addition to affecting the ANS via the lung, it is also possible that PM or its components

25   could directly attack the myocardium. There is substantial evidence that chronic exposure to

26   fibers encountered in the workplace (e.g., asbestos) result in deposition of fibers in organs other

27   than the lung. Some recent studies have suggested that ultrafine PM may exit the lung and

28   deposit in other organs, including the liver and heart. So far these studies have used sources of

29   particles not naturally found in the air (e.g., silver colloid, latex) so it is not yet clear to what

30   extent PM actually leaves the lung or, if it does, how it interacts directly with the heart.

31   However, there is some evidence of direct changes in the myocardium following PM exposure.

1   For example, rats exposed to ROFA, which is made up mostly of soluble transition metals, have

2   increased pro-inflammatory cytokine expression in the left ventricle. In another study, dogs

3   living in highly-polluted Mexico City had histopathology changes in heart tissue compared with

4   dogs living in areas with low air pollution. Substantial deposits of particulate matter could be

5   seen throughout the myocardium in the Mexico City dogs. Though preliminary, these

6   observations point to a need for additional work to better define PM-induced changes in

7   myocardial tissue.

8   Acute coronary events frequently occur as a result of thrombus formation in the site of a

9   ruptured atherosclerotic plaque. Increased levels of clotting and coagulation factors, platelet

10 aggregability, and blood viscosity, together with reduced fibrinolytic activity and endothelial cell

11 dysfunction can promote a pro-coagulant state which could potentially contribute to thrombus

12 formation. C reactive protein, a marker of systemic inflammation which correlates with some

13 cardiac events, is positively associated with PM in several panel studies. Some of these studies

14 also report associations between PM and enhanced blood viscosity or increased fibrinogen, a

15 known risk factor for ischemic heart disease. Controlled human and animal exposure studies

16 have also reported that exposure to CAPS (in humans) or ROFA (in animals) results in increased

17 levels of blood fibrinogen. These studies suggest that PM may alter the coagulation pathways in

18 such a way as to trigger cardiovascular events in susceptible individuals.

19   Panel studies have also reported associations between PM and changes in white blood cells,

20 although these findings are not easy to interpret since some studies report positive associations

21 while others report negative associations. Animal studies are similarly unclear, with some

22 studies (rodents exposed to CAPS) reporting increased numbers of blood platelets and white

23 blood cells and others (rodents exposed to ROFA) reporting decreased numbers of white blood

24 cells. In one study, rabbits instilled with colloidal carbon had an increase in neutrophils released

25 from the bone marrow. The same research group found an association between PM and elevated

26 band neutrophil counts (a marker for bone marrow precursor release) in humans exposed to high

27 levels of carbon from biomass burning during the 1997 Southeast Asian smoke-haze episodes.

28   Endothelial cell dysfunction may contribute to myocardial ischemia in some susceptible

29 populations. The vascular endothelium secretes multiple factors that control vascular tone,

30 modulate platelet activity, and influence thrombogenesis. A recent study has reported endothelial

31 cell dysfunction in humans exposed to CAPS, as measured by dilation of the brachial artery.

1   This vasoconstriction could be caused by an increase in circulating endothelin-1, which has been

2   described in rats exposed to PM.

3   Taken as a whole, these studies are difficult to interpret but clearly indicate that PM can

4   affect the circulatory system. However, a complete understanding of the pathways by which very

5   small concentrations of inhaled ambient PM can produce vascular changes that can contribute to

6   increased mortality/morbidity remains to be more fully elucidated.

7

8

9.12 HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER OBSERVED IN POPULATION STUDIES

11   *How are exposures to ambient PM quantitatively related to increased risks of health effects*

12   *(mortality/morbidity) among general human populations and susceptible subgroups?*

13

9.12.1 Introduction

15   This section assesses available scientific evidence regarding the physiologic and health

16   effects of exposure to ambient PM as observed in epidemiologic (human population) studies.

17   The main objectives of this evaluation are (1) to summarize and evaluate strengths and

18   limitations of available epidemiologic findings; (2) to summarize quantitative relationships

19   between ambient PM exposures and increased human health risks; (3) to assess the biomedical

20   coherence of findings across studied endpoints; and (4) to note the increased biologic plausibility

21   of the available epidemiologic evidence in light of (a) linkages between specific PM components

22   and health effects and (b) various dosimetric, mechanistic, and pathophysiologic considerations

23   discussed earlier in this chapter.

24   Numerous epidemiologic studies have shown statistically significant associations of

25   ambient PM levels with a variety of human health endpoints, including mortality, hospital

26   admissions, emergency department visits, other medical visits, respiratory illness and symptoms

27   measured in community surveys, and physiologic changes in pulmonary function. Associations

28   have been consistently observed between both short- and long-term PM exposure and these

29   endpoints. The general internal consistency of the epidemiologic database and available findings

30   demonstrate well that notable human health effects are associated with exposures to ambient PM

31   at concentrations currently found in many geographic locations across the United States.

1   However, many difficulties still exist with regard to delineating the magnitudes and variabilities

2   of risk estimates for ambient PM, the ability to attribute observed health effects to specific PM

3   constituents, the time intervals over which PM health effects are manifested, the extent to which

4   findings in one location can be generalized to other locations, and the nature and magnitude of

5   the overall public health risk imposed by ambient PM exposure.

6   The etiology of most air pollution-related health outcomes is highly multifactorial, and the

7   impact of ambient air pollution exposure on these outcomes is often small in comparison to that

8   of other etiologic factors (e.g., smoking). Also, ambient PM exposure usually is accompanied by

9   exposure to many other pollutants, and PM itself is composed of numerous physical/chemical

10   components. Assessment of the health effects attributable to PM and its constituents within an

11   already-subtle total air pollution effect is difficult even with well-designed studies. Indeed,

12   statistical partitioning of separate pollutant effects may not characterize fully the etiology of

13   effects that actually depend on simultaneous exposure to multiple air pollutants. In this regard,

14   several viewpoints existed at the time of the 1996 PM AQCD regarding how best to interpret the

15   epidemiology data: one saw the PM exposure indicators as surrogate measures of complex

16   ambient air pollution mixtures and the reported PM-related effects as representative of those of

17   the overall mixture; another held that reported PM-related effects are attributable to PM

18   components (per se) of the air pollution mixture and reflect independent PM effects; and a third

19   viewpoint holds that PM can be viewed both as a surrogate indicator, as well as a specific cause

20   of health effects.

21   Several other key issues and problems also must be considered when attempting to interpret

22   the data reviewed in this document. For example, although the epidemiology data provide strong

23   support for the associations mentioned above, questions remain regarding potential underlying

24   mechanisms. Although much progress has been made toward identification of anatomic sites at

25   which particles trigger specific health effects and elucidation of biological mechanisms that

26   underlie induction of such effects, this area of scientific inquiry is still at an early stage. Still,

27   compared to the lack of much solid evidence available in the 1996 PM AQCD, there now is a

28   stronger basis for assessing biologic plausibility of the epidemiologic observations given notable

29   improvement in conceptual formulation of reasonable mechanistic hypotheses and evidence

30   bearing on such hypotheses. New evidence related to several hypotheses was discussed earlier

31   with regard to possible mechanisms by which ambient PM may exert human health effects,

1   which tends to support the likelihood of a causal relationship between low ambient

2   concentrations of PM and observed increased mortality or morbidity risks. At the same time,

3   much still remains to be done to identify more confidently specific causal agents among typical

4   ambient PM constituents.

5

9.12.2 Community-Health Epidemiologic Evidence for Ambient Particulate Matter Effects

8   In recent years, epidemiologic studies showing associations of ambient air pollution

9   exposure with mortality, exacerbation of preexisting illness, and pathophysiologic changes have

10   increased concern about the extent to which exposure to ambient air pollution exacerbates or

11   causes harmful health outcomes at pollutant concentrations now experienced in the United

12   States. The PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM

13   as a likely key contributor to mortality and morbidity effects observed epidemiologically to be

14   associated with ambient air pollution exposures. New studies appearing since the 1996 PM

15   AQCD are important in extending results of earlier studies to many more cities and in confirming

16   earlier findings.

17   In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant

18   health effects have been observed quite consistently, frequently being statistically significant at

19   $p \leq 0.05$. If ambient air pollution promotes or produces harmful health effects, relatively small

20   effect estimates from current PM concentrations in the United States and many other countries

21   would generally be expected on biological and epidemiologic grounds. Also, magnitudes and

22   significance levels of observed air pollution-related effects estimates would be expected to vary

23   somewhat from place to place, if the observed epidemiologic associations denote actual effects,

24   because (a) not only would the complex mixture of PM vary from place to place, but also

25   (b) affected populations may differ in characteristics that could affect susceptibility to air

26   pollution health effects. Such characteristics include sociodemographic factors, underlying

27   health status, indoor-outdoor activities, diet, medical care access, exposure to risk factors other

28   than ambient air pollution (such as extreme weather conditions), and variations in factors (e.g.,

29   air-conditioning) affecting human exposures to ambient-generated PM.

30   Although it has been argued by some that the observed effects estimates for ambient air

31   pollution are not sufficiently constant across epidemiologic studies and that epidemiologic

1   studies are trustworthy only if they show relatively large effects estimates (e.g., large relative

2   risks), these arguments have only limited weight in relation to ambient air pollution studies.

3   Also, in any large population exposed to ambient air pollution, even a small relative risk for a

4   widely prevalent health disorder could result in a substantial public health burden attributable to

5   air pollution exposure, as was noted earlier (see Section 9.10).

6   As noted above, small health effects estimates generally have been observed for ambient air

7   pollutants, as would be expected on biological and epidemiologic grounds. In contrast to effects

8   estimates derived for the 1952 London smog episode with relative risk (RR) exceeding 4.0 (i.e.,

9   400% increase over baseline) for extremely high (≥ 2 mg/m^3) ambient PM concentrations, effects

10   estimates in most current epidemiology studies at distinctly lower PM concentrations (often

11   ≤ 100 μg/m^3) are relatively small. The statistical estimates (1) are more often subject to small

12   (but proportionately large) differences in estimated effects of PM and other pollutants; (2) may

13   be sensitive to a variety of methodological choices; and (3) sometimes may not be statistically

14   significant, reflecting low statistical power of the study design to detect a small but real effect.

15   The ambient atmosphere contains numerous air pollutants, and it is important to continue to

16   recognize that health effects associated statistically with any single pollutant may actually be

17   mediated by multiple components of the complex ambient mix. Specific attribution of effects to

18   any single pollutant may therefore be overly simplistic. Particulate matter is one of many air

19   pollutants derived from combustion sources, including mobile sources. These pollutants include

20   PM, carbon monoxide, sulfur oxides, nitrogen oxides, and ozone, all of which have been

21   considered in various epidemiologic studies to date. Many volatile organic compounds (VOCs)

22   or semivolatile compounds (SVOCs) also emitted by combustion sources or formed in the

23   atmosphere have not yet been systematically considered in relation to noncancer health outcomes

24   usually associated with exposure to criteria air pollutants. In many newly available

25   epidemiologic studies, harmful health outcomes are often associated with multiple combustion-

26   related or mobile-source-related air pollutants, and some investigators have raised the possibility

27   that PM may be a key surrogate or marker for a larger subset of the overall ambient air pollution

28   mix. This possibility takes on added potential significance to the extent that ambient aerosols

29   indeed may not only exert health effects directly attributable to their constituent components, per

30   se, but also serve as carriers for more efficient delivery of water soluble toxic gases (e.g., O_3,

31   NO_2, SO_2) deeper into lung tissue, as noted earlier in Section 9.8.4. This suggests that airborne

1   particle effects may be enhanced by the presence of other toxic agents or mistakenly attributed to

2   them if their respective concentrations are highly correlated temporally. Thus, although

3   associations of PM with harmful effects continue to be observed consistently across most new

4   studies, the newer findings do not fully resolve issues concerning relative contributions to the

5   observed epidemiologic associations of (a) PM acting alone, (b) PM acting in combination with

6   gaseous co-pollutants, (c) the gaseous pollutants per se, and (d) the overall ambient pollutant

7   mix.

8   It seems likely that, for pollutants whose concentrations are not highly correlated, effects

9   estimates in multipollutant models would be more biologically and epidemiologically sound than

10   those in single-pollutant models, although it is conceivable that single-pollutant models also

11   might be credible if independent biological plausibility evidence supported designation of PM or

12   some other single pollutant as likely being the key toxicant in the ambient pollutant mix

13   evaluated. Because neither of these possibilities have been definitively demonstrated and there is

14   not yet full scientific consensus as to optimal interpretation of modeling outcomes for time

15   series-air pollution studies, the choice of appropriate effects estimates to employ in risk

16   assessments for ambient PM effects remains a difficult issue. Issues related to confounding by

17   co-pollutants, along with issues related to time scales of exposure and response and

18   concentration-response function, still apply to new epidemiologic studies relating concentrations

19   of PM or correlated ambient air pollutants to hospital admissions, exacerbation of respiratory

20   symptoms, and asthma in children, to reduced pulmonary function in children and adults, and to

21   changes in heart rate, and heart rate variability in adults. However, with considerable new

22   experimental evidence now in hand, it is possible to hypothesize various ways in which ambient

23   exposure to PM acting alone or in combination with others could plausibly be involved in the

24   complex chain of biological events leading to harmful health effects in the human population.

25   This newer experimental evidence, coupled with new exposure analyses results, add considerable

26   support for interpreting the epidemiologic findings discussed below as likely being indicative of

27   causal relationships between exposures to ambient PM and consequent associated increased

28   morbidity and mortality risks.

29

30

31

1   **9.12.2.1 Short-Term Particulate Matter Exposure Effects on Mortality**

2   This section focuses primarily on discussion of short-term PM exposure effects on

3   mortality, but also highlights some morbidity effects in relation to the mortality findings.

4   Morbidity effects are discussed more fully after discussion of long-term mortality effects in the

5   section following this one.

6

7   *Summary of Previous Findings on Short-Term Particulate Matter Exposure-Mortality Effects*

8   Time series mortality studies reviewed in the 1996 PM AQCD provided strong evidence

9   that ambient PM air pollution is associated with increased daily mortality. The 1996 PM AQCD

10   summarized about 35 PM-mortality time series studies published between 1988 and 1996. The

11   available information from those studies was consistent with the hypothesis that PM is a causal

12   agent in the mortality impacts of air pollution. The PM_{10} relative risk estimates derived from the

13   PM_{10} studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h

14   average of PM_{10} is associated with an increased risk of premature total mortality (total deaths

15   minus accidents and injuries) mainly on of the order of relative risk (RR) = 1.025 to 1.05 (i.e.,

16   2.5 to 5.0% excess risk) in the general population, with statistically significant increases being

17   reported more broadly across the range of 1.5 to 8.5% per 50 $\mu g/m^3$ PM_{10}. Higher relative risks

18   were indicated for the elderly and for those with preexisting respiratory conditions. Also, based

19   on the then recently published Schwartz et al. (1996) analysis of Harvard Six City data, the 1996

20   PM AQCD found the relative risk for excess total mortality in relation to 24-h fine-particle

21   concentrations to be in the range of RR = 1.026 to 1.055 per 25 $\mu g/m^3$ $PM_{2.5}$ (i.e., 2.6 to 5.5%

22   excess risk per 25 $\mu g/m^3$ $PM_{2.5}$). Relative risk estimates for morbidity and mortality effects

23   associated with standard increments in ambient PM_{10} concentrations and for fine-particle

24   indicators (e.g., $PM_{2.5}$, sulfates, etc.) were presented in Chapters 12 and 13 of the 1996 PM

25   AQCD (see Appendix 9A), and those effect estimates are updated below in light of the extensive

26   newly available evidence discussed in Chapter 8 of this document.

27   Although numerous studies reported PM-mortality associations, several important issues

28   needed to be addressed in interpreting those relative risks. The 1996 PM AQCD extensively

29   discussed the following critical issues: (1) seasonal confounding and effect modification,

30   (2) confounding by weather, (3) confounding by co-pollutants, (4) measurement error,

1   (5) functional form and threshold, (6) harvesting and life shortening; and (7) the roles of specific
2   PM components.

3   Season-specific analyses are often not feasible because of small magnitudes of expected
4   effect size or small sample sizes (low power) available for some studies. Some studies had
5   earlier suggested possible season-specific variations in PM coefficients, but it was not clear if
6   these were caused by peak variations in PM effects from season to season, varying extent of PM
7   correlations with other co-pollutants, or weather factors during different seasons. The likelihood
8   of PM effects being accounted for mainly by weather factors was addressed by various methods
9   that controlled for weather variables in most studies (including some involving sophisticated
10 synoptic weather pattern evaluations), and that possibility was found to be very unlikely.

11   Many early PM studies considered at least one co-pollutant in the mortality regression, and
12 an increasing number have examined multiple pollutants. Usually, when PM indices were
13 significant in single-pollutant models, addition of a co-pollutant diminished the PM effect size
14 somewhat, but did not eliminate PM associations. In multiple-pollutant models performed by
15 season, the PM coefficients became less stable, again possibly because of varying correlations of
16 PM with co-pollutants among seasonal or smaller sample sizes. However, in many studies, PM
17 indices showed the highest significance in both single- and multiple-pollutant models. Thus,
18 PM-mortality associations did not appear to be seriously distorted by co-pollutants.

19   Interpretation of the relative significance of each pollutant in mortality regression in
20 relation to its relative causal strength was difficult, however, because of lack of quantitative
21 information on pertinent exposure measurement errors among the air pollutants. Measurement
22 errors can influence the size and significance of air pollution coefficients in time series
23 regression analyses, an issue also important in assessing confounding among multiple pollutants,
24 because the varying extent of such errors among pollutants may influence corresponding relative
25 significance. The 1996 PM AQCD discussed several types of exposure measurement and
26 characterization errors, including site-to-site variability and site-to-person variability. These
27 errors are thought to bias the estimated PM coefficients downward in most cases, but there was
28 insufficient quantitative information available at the time to allow estimation of such bias.

29   The 1996 PM AQCD also reviewed evidence for threshold and various other functional
30 forms of short-term PM mortality associations. Some studies indicated that associations were
31 seen monotonically to even below the PM standards. It was considered difficult, however, to

1   statistically identify a threshold from available data because of low data density at lower ambient

2   PM concentrations, potential influence of measurement error, and adjustments for other

3   covariates. Thus, use of relative risk (rate ratio) derived from log-linear Poisson models was

4   deemed adequate.

5   The extent of prematurity of death, i.e., mortality displacement (or harvesting) in observed

6   PM-mortality associations has important public health policy implications. At the time of the

7   1996 PM AQCD review, only a few studies had investigated this issue. Although one of the

8   studies suggested that the extent of such prematurity might be only a few days, this may not be

9   generalized because this estimate was obtained for identifiable PM episodes. Insufficient

10 evidence then existed to suggest the extent of prematurity for nonepisodic periods, from which

11 most of the recent PM relative risks were derived.

12   Only a few PM-mortality studies had analyzed fine particles and chemically specific

13 components of PM. The Harvard Six Cities Study (Schwartz et al., 1996) analyzed size-

14 fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+).

15 The results suggested that $PM_{2.5}$ was associated most significantly with mortality among the PM

16 components. Although H^+ was not significantly associated with mortality in this and earlier

17 analyses, the smaller sample size for H^+ than for other PM components made direct comparison

18 difficult. Also, certain respiratory morbidity studies showed associations between hospital

19 admissions and visits with components of PM in the fine-particle range. Thus, the 1996 PM

20 AQCD concluded that there was adequate evidence to suggest that fine particles play especially

21 important roles in observed PM mortality effects.

22   Overall, then, the outcome of assessment of the above key issues in the 1996 PM AQCD

23 can be thusly summarized: (1) observed PM effects are not likely seriously biased by inadequate

24 statistical modeling (e.g., control for seasonality); (2) observed PM effects are not likely

25 significantly confounded by weather; (3) observed PM effects may be confounded or modified to

26 some extent by co-pollutants, and such extent may vary from season to season; (4) determining

27 the extent of confounding and effect modification by co-pollutants requires knowledge of relative

28 exposure measurement/characterization error among pollutants (there was not sufficient

29 information on this); (5) no clear evidence for any threshold for PM-mortality associations was

30 reported (statistically identifying a threshold from existing data also was considered difficult, if

31 not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was

1   reported for episodic periods (no study was conducted to investigate harvesting in nonepisodic

2   U.S. data); and (7) only a relatively limited number of studies suggested a causal role of fine

3   particles in PM-mortality associations, but in light of historical data, biological plausibility, and

4   results from morbidity studies, a greater role for fine particles than coarse particles was suggested

5   as being likely.

6

7   *Updated Epidemiologic Findings for Short-Term Ambient Particulate Matter*
8   *Exposure Effects on Mortality*

9   With regard to updating the assessment of PM effects in light of new epidemiologic

10   information published since the 1996 PM AQCD, the most salient key points on relationships

11   between short-term PM exposure and mortality (drawn from Chapter 8 discussions in this

12   document) can be summarized as follows.

13   Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality

14   analyses, several of which investigated multiple cities using consistent data analytical

15   approaches. With only few exceptions, the estimated mortality relative risks in these studies are

16   generally positive, many are statistically significant, and they generally comport well with

17   previously reported PM-mortality effects estimates delineated in the 1996 PM AQCD. There are

18   also now numerous additional studies demonstrating associations between short-term (24-h) PM

19   exposures and various morbidity endpoints.

20   Several new studies conducted time series analyses in multiple cities. The major advantage

21   of these studies over meta-analyses for multiple "independent" studies is the consistency in data

22   handling and model specifications, thus eliminating variation in results attributable to study

23   design. Also, many of the cities included in these studies were ones for which no earlier time

24   series analyses had been conducted. Therefore, unlike regular meta-analysis, they likely do not

25   suffer from omission of negative studies caused by publication bias. Furthermore, any spatial or

26   geographic variability of air pollution effects can be systematically evaluated in such multi-city

27   analyses.

28

29   **PM_{10} Effect Size Estimates.** In the NMMAPS (Samet et al., 2000a,b) analysis of the

30   90 largest U.S. cities, the combined nationwide relative risk estimate was about a 2.3% increase

31   in total mortality per 50-μg/m^3 increase in PM_{10}. The NMMAPS effect size estimates did vary

1   somewhat by U.S. region (see Figures 8-3 and 8-5), with the largest estimate being for the

2   Northeast (4.5% for a 1-day lag, the lag typically showing maximum effect size for most U.S.

3   regions). Various other U.S. multi-city analyses, as well as single-city analyses, obtained PM_{10}

4   effect sizes mainly in the range of 2.5 to 5.0% per 50-μg/m^3 increase in PM_{10}. There is some

5   evidence that, if the effects over multiple days are considered, the effect size may be larger.

6   What heterogeneity existed for the estimated PM_{10} risks across NMMAPS cities could not be

7   explained with the city-specific explanatory variables (e.g., as the mean levels of pollution and

8   weather), mortality rate, sociodemographic variables (e.g., median household income),

9   urbanization, or variables related to measurement error.

10   Original results reported for the multi-city APHEA study showed generally consistent

11   associations between mortality and both SO_2 and PM indices in western European cities, but not

12   for central and eastern European cities. More recent studies from APHEA II analyses, however,

13   found analogous increased risks to be associated with PM exposures in central and eastern

14   Europe as in western European cities. The pooled estimate of PM_{10}-mortality relative risks for

15   European cities comport well with estimates derived from U.S. data.

16   Certain other individual-city studies using similar methodology in analyses for each city

17   (but not generating combined overall pooled effect estimates) also report variations in PM effect

18   size estimates between cities and in their robustness to inclusion of gaseous copollutants in

19   multi-pollutant models. Thus, one cannot entirely rule out that real differences may exist in

20   excess risk levels associated with varying size distributions, number, or mass of the chemical

21   constituents of ambient PM; the combined influences of varying co-pollutants present in the

22   ambient air pollution mix from location to location or season to season; or to variations in the

23   relationship between exposure and ambient PM concentration.

24   Nevertheless, there still appears to be reasonably good consistency among the results

25   derived from those several new multi-city studies providing pooled analyses of data combined

26   across multiple cities (thought to yield the most precise effect size estimates). Such analyses

27   indicate the percent excess total (nonaccidental) deaths estimated per 50 μg/m^3 increase in 24-h

28   PM_{10} to be 2.3% in the 90 largest U.S. cities (4.5% in the Northeast region); 3.4% in 10 U.S.

29   cities; 3.5% in the eight largest Canadian cities; and about 2.0% in European cities (using PM_{10}

30   = TSP*0.55). These combined estimates are reasonably consistent with the range of PM_{10}

31   estimates previously reported in the 1996 PM AQCD (i.e., 1.5 to 8.5% per 50 μg/m^3 PM_{10}).

1   These and other excess risk estimates from many other individual-city studies comport well with

2   a number of new studies confirming increased cause-specific cardiovascular- and respiratory-

3   related mortality, and those noted below as showing ambient PM associations with increased

4   cardiovascular and respiratory hospital admissions and medical visits.

5

6   **Fine and Coarse Particle Effect Size Estimates.** Table 9-14 summarizes effects

7   estimates (RR values) for increased mortality and/or morbidity associated with variable

8   increments in short-term (24-h) exposures to ambient fine particles indexed by various fine PM

9   indicators ($PM_{2.5}$, sulfates, H^+, etc.) in U.S. and Canadian cities. Table 9-15 shows analogous

10   effect size estimates for inhalable thoracic fraction coarse particles (i.e., $PM_{10-2.5}$). In both tables,

11   studies that were highlighted in comparable tables in the 1996 PM AQCD are indicated by

12   italics. For purposes of comparison across studies, results of single-pollutant models are

13   presented in these tables; co-pollutant model results are presented and discussed in more detail in

14   Chapter 8.

15   The effect size estimates derived for $PM_{2.5}$ as an ambient fine particle indicator (especially

16   those based on directly measured versus estimated $PM_{2.5}$ levels) generally appear to fall in the

17   range of 2.0 to 8.5% increase in total (nonaccidental) deaths per 25-$\mu g/m^3$ increment in 24-h

18   $PM_{2.5}$ for U.S. and Canadian cities. Cause-specific effects estimates appear to fall mainly in the

19   range of 3.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for cardiovascular or combined cardiorespiratory

20   mortality and 2.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for respiratory mortality in U.S. cities.

21   In the 1996 PM AQCD, there was only one study, the Harvard Six Cities study, in which

22   the relative importance of fine and coarse particles was examined. That study suggested that fine

23   particles, but not coarse particles, were associated with daily mortality. Now, more than

24   10 studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality (see

25   Figure 9-25). Although some of these studies (e.g., the Santa Clara County, CA, analysis and the

26   eight largest Canadian cities analysis) suggest that $PM_{2.5}$ is more important than $PM_{10-2.5}$ in

27   predicting mortality fluctuations, several others (e.g., the Mexico City and Santiago, Chile

28   studies) seem to suggest that $PM_{10-2.5}$ may be as important as $PM_{2.5}$ in certain locations (some

29   shown to date being drier, more arid areas). Seasonal dependence of PM components'

30   associations observed in some of the locations (e.g., higher coarse [$PM_{10-2.5}$] fraction estimates for

31   summer than winter in Santiago, Chile) hint at possible contributions of biogenic materials (e.g.,

TABLE 9-14. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS (PM$_{2.5}$, SO$_4^=$, H$^+$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	Reported PM Levels Mean (Min, Max)***
Acute Total Mortality			
Six City:[A]			
Portage, WI	*PM$_{2.5}$*	*1.030 (0.993, 1.071)*	*11.2 (±7.8)*
Topeka, KS	*PM$_{2.5}$*	*1.020 (0.951, 1.092)*	*12.2 (±7.4)*
Boston, MA	*PM$_{2.5}$*	*1.056 (1.038, 1.0711)*	*15.7 (±9.2)*
St. Louis, MO	*PM$_{2.5}$*	*1.028 (1.010, 1.043)*	*18.7 (±10.5)*
Kingston/Knoxville, TN	*PM$_{2.5}$*	*1.035 (1.005, 1.066)*	*20.8 (±9.6)*
Steubenville, OH	*PM$_{2.5}$*	*1.025 (0.998, 1.053)*	*29.6 (±21.9)*
Overall Six-City Results	*PM$_{2.5}$*	*1.015 (1.011, 1.019)*	*Median 14.7*
Six U.S. Cities[B]	PM$_{2.5}$	Overall 1.010 (1.028, 1.053) Mobile 1.087 (1.042, 1.134) Coal 1.028 (1.006, 1.050) Crustal 0.944 (0.863, 1.032)	Means 11.3-30.5
Santa Clara County, CA[C]	PM$_{2.5}$	1.13 (p < 0.01)	13 (2, 105)
Buffalo, NY[D]	SO$_4^=$	1.034 (1.009, 1.062)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[E]	PM$_{2.5}$	1.042 (p < 0.055)	17.28 (-0.6, 72.6)
Detroit, MI[F]	PM$_{2.5}$	1.031 (0.994, 1.069)	18 (6, 86)
Phoenix, AZ[G]	PM$_{2.5}$	1.030 (1.000, 1.076)	13.0 (0, 42)
Phoenix, AZ[H]	PM$_{2.5}$	(>25 μg/m^3) 2.868 (1.126, 7.250) (<25 μg/m^3) 0.779 (0.610, 0.995)	NR
Los Angeles, CA[I]	PM$_{2.5}$	1.06 (NS, from figure)	22 (4, 86)
San Bernadino and Riverside Counties, CA[J]	Est. PM$_{2.5}$	1.003 (0.992, 1.015)	32.5 (9.3, 190.1)
Coachella Valley, CA[K]	PM$_{2.5}$	1.118 (1.013, 1.233)	16.8 (5, 48)
Boston, MA[L]	PM$_{2.5}$	1.053 (1.018, 1.090)	15.6 (±9.2)
Three New Jersey Cities:[M]			
Newark, NJ	PM$_{2.5}$	1.043 (1.028, 1.059)	42.1 (±22.0)
Camden, NJ	PM$_{2.5}$	1.057 (1.001, 1.115)	39.9 (±18.0)
Elizabeth, NJ	PM$_{2.5}$	1.018 (0.946, 1.095)	37.1 (±19.8)
Eight Canadian Cities[N]	PM$_{2.5}$	1.030 (1.011, 1.050)	13.3 (max 86)

TABLE 9-14 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS (PM$_{2.5}$, SO$_4^=$, H$^+$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR ($\pm$ CI)** per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	Reported PM Levels Mean (Min, Max)***
Toronto, Canada[O]	Est. PM$_{2.5}$	1.048 (1.033, 1.064)	18.0 (8, 90)
Montreal, Canada[P]	PM$_{2.5}$	1.058 (1.034, 1.083)	17.4 (2.2, 72.0)
Cause-Specific Mortality			
Cardiorespiratory:			
Three New Jersey Cities:[M]			
Newark, NJ	PM$_{2.5}$	1.051 (1.031, 1.072)	42.1 ($\pm$22.0)
Camden, NJ	PM$_{2.5}$	1.062 (1.006, 1.121)	39.9 ($\pm$18.0)
Elizabeth, NJ	PM$_{2.5}$	1.023 (0.950, 1.101)	37.1 ($\pm$19.8)
Total Cardiovascular:			
Santa Clara County, CA[C]	PM$_{2.5}$	1.07 (p > 0.05)	13 (2, 105)
Buffalo, NY)[D]	SO$_4^=$	1.040 (0.995, 1.088)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[F] (seven-county area)	PM$_{2.5}$	1.028 (p < 0.055)	17.28 (-0.6, 72.6)
Detroit, MI[G]	PM$_{2.5}$	1.032 (0.977, 1.089)	18 (6, 86)
Phoenix, AZ[H]	PM$_{2.5}$	1.187 (1.057, 1.332)	13.0 (0, 42)
Los Angeles, CA[I]	PM$_{2.5}$	1.027 (1.003, 1.048)	22 (4, 86)
San Bernadino and Riverside Counties, CA[J]	Est. PM$_{2.5}$	1.007 (0.997, 1.017)	32.5 (9.3, 190.1)
Coachella Valley, CA[K]	PM$_{2.5}$	1.086 (0.937, 1.258)	16.8 (5, 48)
Cerebrovascular:			
Los Angeles, CA[I]	PM$_{2.5}$	1.036 (0.994, 1.080)	22 (4, 86)
Total Respiratory:			
Santa Clara County, CA[C]	PM$_{2.5}$	1.13 (p > 0.05)	13 (2, 105)
Buffalo, NY[D]	SO$_4^=$	1.108 (1.007, 1.219)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[F] (seven-county area)	PM$_{2.5}$	1.014 (p > 0.055)	17.28 (-0.6, 72.6)
Detroit, MI[G]	PM$_{2.5}$	1.023 (0.897, 1.166)	18 (6, 86)
San Bernadino and Riverside Counties, CA[J]	Est. PM$_{2.5}$	1.021 (0.997, 1.045)	32.5 (9.3, 190.1)

TABLE 9-14 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR ($\pm$ CI)** per 25-μg/m³ PM Increase or 15-μg/m³ $SO_4^=$ Increase or 75-nmol/m³ H^+ increase	Reported PM Levels Mean (Min, Max)***
COPD:			
Los Angeles, CA[I]	$PM_{2.5}$	1.027 (0.966, 1.091)	22 (4, 86)
Increased Hospitalization			
Ontario, Canada[Q]	*$SO_4^=$*	*1.03 (1.02, 1.04)*	*R = 3.1-8.2*
Ontario, Canada[R]	*$SO_4^=$* *O_3*	*1.03 (1.02, 1.04)* *1.03 (1.02, 1.05)*	*R = 2.0-7.7*
NYC/Buffalo, NY[S]	*$SO_4^=$*	*1.05 (1.01, 1.10)*	*NR*
Toronto, Canada[S]	*H^+ (Nmol/m³)* *$SO_4^=$* *$PM_{2.5}$*	*1.16 (1.03, 1.30)** *1.12 (1.00, 1.24)* *1.15 (1.02, 1.28)*	*28.8 (NR/391)* *7.6 (NR, 48.7)* *18.6 (NR, 66.0)*
Total Respiratory:			
King County, WA[T]	PM_1	1.058 (1.011, 1.110)	NR
Toronto, Canada[U]	$PM_{2.5}$	1.085 (1.034, 1.138)	16.8 (1, 66)
Buffalo, NY[D]	$SO_4^=$	1.082 (1.042, 1.128)	61.7 (0.78, 390.5) nmol/m³
Montreal, Canada[V]	$PM_{2.5}$	1.239 (1.048, 1.428)	Summer 93 12.2 (max 31)
Montreal, Canada[W]	$PM_{2.5}$	1.137 (0.998, 1.266)	18.6 (SD 9.3)
St. John, Canada[X]	$PM_{2.5}$	1.057 (1.006, 1.110)	Summer 93 8.5 (max 53.2)
Pneumonia:			
Detroit, MI[F]	$PM_{2.5}$	1.125 (1.037, 1.220)	18 (6, 86)
Respiratory infections:			
Toronto, Canada[U]	$PM_{2.5}$	1.108 (1.072, 1.145)	18.0 (max 90)
COPD:			
Atlanta, GA[Z]	$PM_{2.5}$	1.124 (0.921, 1.372)	19.4 ($\pm$9.35)
Detroit, MI[F]	$PM_{2.5}$	1.055 (0.953, 1.168)	18 (6, 86)
King County WA[AA]	$PM_{2.5}$	1.064 (1.009, 1.121)	18.1 (3, 96)
Los Angeles, CA[BB]	$PM_{2.5}$	1.051 (1.009, 1.094) (65+ y.o.) 1.04 (0.99, 1.09) ((0-19 y.o.) 1.06 (1.02, 1.09) (20-64 y.o.)	Median 22 (4, 86)
Toronto, Canada[Y]	$PM_{2.5}$	1.048 (0.998, 1.100)	18.0 (max 90)

TABLE 9-14 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS (PM$_{2.5}$, SO$_4^=$, H$^+$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	Reported PM Levels Mean (Min, Max)***
Asthma:			
Atlanta, GA[Z]	PM$_{2.5}$	1.023 (0.852, 1.227)	19.4 (±9.35)
Seattle, WA[CC]	PM$_{2.5}$	1.087 (1.033, 1.143)	16.7 (6, 32)
Seattle, WA[DD]	Est. PM$_{2.5}$	1.445 (1.217, 1.714)	4.8 (1.2, 32.4)
Toronto, Canada[Y]	PM$_{2.5}$	1.064 (1.025, 1.106)	18.0 (max 90)
Total Cardiovascular:			
Atlanta, GA[Z]	PM$_{2.5}$	1.061 (0.969, 1.162)	19.4 (±9.35)
Buffalo, NY[D]	SO$_4^=$	1.015 (0.987, 1.043)	61.7 (0.78, 390.5) nmol/m^3
Los Angeles, CA[EE]	PM$_{2.5}$	(65+) 1.043 (1.025, 1.061) (<65) 1.035 (1.018, 1.053)	Median 22 (4, 86)
St. John, Canada[X]	PM$_{2.5}$	1.151 (0.998, 1.328)	Summer 93 8.5 (max 53.2)
Toronto, Canada[U]	PM$_{2.5}$	1.072 (0.994, 1.156)	16.8 (1, 66)
Ischemic Heart Disease:			
Detroit, MI[F]	PM$_{2.5}$	1.043 (0.986, 1.104)	18 (6, 86)
Toronto, Canada[Y]	PM$_{2.5}$	1.080 (1.054, 1.108)	18.0 (max 90)
Dysrhythmias:			
Atlanta, GA[Z]	PM$_{2.5}$	1.061 (0.874, 1.289)	19.4 (±9.35)
Detroit, MI[F]	PM$_{2.5}$	1.032 (0.934, 1.140)	18 (6, 86)
Toronto, Canada[Y]	PM$_{2.5}$	1.061 (1.019, 1.104)	18.0 (max 90)
Heart Failure:			
Detroit, MI[F]	PM$_{2.5}$	1.091 (1.023, 1.162)	18 (6, 86)
Toronto, Canada[Y]	PM$_{2.5}$	1.066 (1.025, 1.108)	18.0 (max 90)
Cerebrovascular:			
Los Angeles, CA[EE]	PM$_{2.5}$	1.015 (0.992, 1.038)	Median 22 (4, 86)
Toronto, Canada[Y]	PM$_{2.5}$	"NEG" reported	18.0 (max 90)
Peripheral circulation diseases:			
Toronto, Canada[Y]	PM$_{2.5}$	"NEG" reported	18.0 (max 90)

TABLE 9-14 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS (PM$_{2.5}$, SO$_4^=$, H$^+$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR ($\pm$ CI)** per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	Reported PM Levels Mean (Min, Max)***
Stroke:			
Detroit, MI[F]	PM$_{2.5}$	1.018 (0.947, 1.095)	18 (6, 86)
Increased Respiratory Symptoms		Odd Ratio (95% CI) per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	
Southern California[FF]	*SO$_4^=$*	*1.48 (1.14, 1.91)*	*R = 2-37*
Six Cities[GG] *(Cough)*	*PM$_{2.5}$* *SO$_4^=$* *H$^+$*	*1.24 (1.00, 1.54)* *1.86 (0.86, 4.03)* *1.19 (0.66, 2.15)*	*18.0 (max 86.0)* *2.5 (max 15.1)* *18.1 (max 371.1) nmol/m^3*
Six Cities[GG] *(Lower Resp. Symp.)*	*PM$_{2.5}$* *SO$_4^=$* *H$^+$*	*1.58 (1.18, 2.10)* *6.82 (2.09, 17.35)* *1.16 (0.10, 13.73)*	*18.0 (max 86.0)* *2.5 (max 15.1)* *18.1 (max 371.1) nmol/m^3*
Uniontown, PA[HH] *(Evening Cough)*	*PM$_{2.5}$*	*1.45 (1.07, 1.97)*	*24.5 (max 88.1)*
Six Cities Reanalyses[KK] *(Lower Resp. Symptoms)* *(Cough)*	*PM$_{2.5}$*	*1.61 (1.20, 2.16)* *1.28 (0.98, 1.67)*	*18.0 (max 86.0)* *2.5 (max 15.1)* *18.1 (max 371.1) nmol/m^3*
Connecticut summer camp[II]	SO$_4^=$	1.71 (1.30, 2.25)	7.0 (1.1, 26.7)
State College, PA[JJ] (Wheeze)	PM$_{2.1}$	1.59 (0.94, 2.71)	23.5 (max 85.8)
State College, PA[JJ] (Cold)	PM$_{2.1}$	1.61 (1.21, 2.17)	23.5 (max 85.8)
State College, PA[JJ] (Cough)	PM$_{2.1}$	1.48 (1.17, 1.88)	23.5 (max 85.8)
Decreased Lung Function		PEFR change (L/min) per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	
Uniontown, PA[HH]	*PM$_{2.5}$*	*PEFR -1.38 (-2.77, 0.02)*	*24.5 (max 88.1)*
Uniontown, PA[KK] (Reanalysis)	PM$_{2.5}$	pm PEFR -1.52, (-2.80, -0.24)	24.5 (max 88.1)
State College, PA[KK] (Reanalysis)	PM$_{2.5}$	pm PEFR -0.93 (-1.88, 0.01)	23.5 (max 85.8)
Connecticut summer camp[II]	SO$_4^=$	PEFR -5.4 (-12.3, 1.52)	7.0 (1.1, 26.7)

TABLE 9-14 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS (PM$_{2.5}$, SO$_4^=$, H$^+$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR ($\pm$ CI)** per 25-μg/m^3 PM Increase or 15-μg/m^3 SO$_4^=$ Increase or 75-nmol/m^3 H$^+$ increase	Reported PM Levels Mean (Min, Max)***
Southwest, VA[LL]	PM$_{2.5}$	am PEFR $-$1.825 ($-$3.45, -0.21)	21.62 (3.48, 59.65)
State College, PA[JJ]	PM$_{2.1}$	pm PEFR $-$0.63 ($-$1.73, 0.44)	23.5 (max 85.8)
Philadelphia, PA[MM]	PM$_{2.5}$	am PEFR $-$3.28 (-6.64, 0.07) pm PEFR $-$0.91 (-4.04, 2.21)	22.2 (IQR 16.2)

*Studies highlighted in the 1996 CD are in italics; new studies in plain text. For purposes of comparison across studies, results of single-pollutant models are presented in these tables; co-pollutant model results are presented and discussed in more detail in Chapter 8.

**Relative Risk (95% Confidence Interval), except for Fairley (1999) and Lipfert et al. (2000), where insufficient data were available to calculate confidence intervals so p-value is given in parentheses.

***Min, Max 24-h PM indicator level shown in parentheses unless otherwise noted as ($\pm$S.D.), NR = not reported, or R = range of values from min-max, no mean value reported.

References:

[A]Schwartz et al. (1996)
[B]Laden et al. (2000)
[C]Fairley (1999)
[D]Gwynn et al. (2000)
[E]Lipfert et al. (2000a)
[F]Lippmann et al. (2000)
[G]Mar et al. (2000)
[H]Smith et al. (2000)
[I]Moolgavkar (2000a)
[J]Ostro (1995)
[K]Ostro et al. (2000)
[L]Schwartz (2000)
[M]Tsai et al. (2000)

[N]Burnett et al. (2000)
[O]Burnett et al. (1998)
[P]Goldberg et al. (2000)
[Q]Burnett et al. (1994)
[R]Burnett et al. (1995)
[S]Thurston et al. (1992, 1994)
[T]Lumley and Heagerty (1999)
[U]Burnett et al. (1997)
[V]Delfino et al. (1997)
[W]Delfino et al. (1998)
[X]Stieb et al. (2000)
[Y]Burnett et al. (1999)
[Z]Tolbert et al. (2000)

[AA]Moolgavkar et al. (2000)
[BB]Moolgavkar (2000b)
[CC]Sheppard et al. (1999)
[DD]Norris et al. (1999)
[EE]Moolgavkar (2000c)
[FF]Ostro et al. (1993)
[GG]Schwartz et al. (1994)
[HH]Neas et al. (1995)
[II]Thurston et al. (1997)
[JJ]Neas et al. (1996)
[KK]Schwartz and Neas (2000)
[LL]Naeher et al. (1999)
[MM]Neas et al. (1999)

TABLE 9-15. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES ($PM_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-μg/m^3 Increase	Reported PM Levels Mean (Min, Max)***
Acute Mortality			
Six Cities:[A]			
Portage, WI	$PM_{10-2.5}$	*1.013 (0.970, 1.058)*	*6.6 (±6.8)*
Topeka, KS	$PM_{10-2.5}$	*0.968 (0.920, 1.015)*	*14.5 (±12.2)*
Boston, MA	$PM_{10-2.5}$	*1.005 (0.985, 1.030)*	*8.8 (±7.0)*
St. Louis, MO	$PM_{10-2.5}$	*1.005 (0.983, 1.028)*	*11.9 (±8.5)*
Kingston/Knoxville, TN	$PM_{10-2.5}$	*1.025 (0.985, 1.066)*	*11.2 (±7.4)*
Steubenville, OH	$PM_{10-2.5}$	*1.061 (1.013, 1.111)*	*16.1 (±13.0)*
Overall Six-City Results	$PM_{10-2.5}$	*1.004 (0.999, 1.010)*	*Median 9.0*
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.013 (0.994, 1.032)	17.9 (0, 149)
Detroit, MI[C]	$PM_{10-2.5}$	1.040 (0.988, 1.094)	13 (4, 50)
Philadelphia, PA[D]	$PM_{10-2.5}$	1.052 (p > 0.055)	6.80 (-20.0, 28.3)
Phoenix, AZ[E]	$PM_{10-2.5}$	1.030 (0.995, 1.066)	33.5 (5, 187)
Phoenix, AZ[F]	$PM_{10-2.5}$	(>25 μg/m^3) 1.185 (1.069, 1.314) (<25 μg/m^3) 1.020 (1.005, 1.035)	NR
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.03 (p > 0.05))	11 (0, 45)
Eight Canadian Cities[H]	$PM_{10-2.5}$	1.018 (0.992, 1.044)	12.9 (max 99)
Cause-Specific Mortality			
Total Cardiovascular:			
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.026 (1.006, 1.045)	17.9 (0, 149)
Detroit, MI[C]	$PM_{10-2.5}$	1.078 (1.000, 1.162)	13 (4, 50)
Philadelphia, PA[D] (seven-county area)	$PM_{10-2.5}$	1.034 (p > 0.055)	6.80 (-20.0, 28.3)
Phoenix, AZ[E]	$PM_{10-2.5}$	1.064 (1.014, 1.117)	33.5 (5, 187)
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.03 (p > 0.05)	11 (0, 45)
Total Respiratory:			
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.026 (1.006, 1.045)	17.9 (0, 149)
Detroit, MI[D]	$PM_{10-2.5}$	1.074 (0.910, 1.269)	13 (4, 50)
Philadelphia, PA[D] (seven-county area)	$PM_{10-2.5}$	1.030 (p > 0.055)	6.80 (-20.0, 28.3)
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.16 (p > 0.05)	11 (0, 45)

TABLE 9-15 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES (PM$_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-μg/m^3 Increase	Reported PM Levels Mean (Min, Max)***
Increased Hospitalization			
Total Respiratory:			
Toronto, Canada[I]	PM$_{10-2.5}$	1.125 (1.052, 1.20)	11.6 (1, 56)
Pneumonia:			
Detroit, MI[C]	PM$_{10-2.5}$	1.119 (1.006, 1.244)	13 (4, 50)
Respiratory infections:			
Toronto, Canada[J]	PM$_{10-2.5}$	1.093 (1.046, 1.142)	12.2 (max 68)
COPD:			
Atlanta, GA[K]	PM$_{10-2.5}$	0.770 (0.493, 1.202)	9.39 (±4.52)
Detroit, MI[C]	PM$_{10-2.5}$	1.093 (0.958, 1.247)	13 (4, 50)
Los Angeles[Q]	PM$_{10-2.5}$	1.17 (1.09, 1.26) (0-19 y.o.) 1.09 (1.03, 1.15) (20-64 y.o.) 1.05 (0.99, 1.11) (65+ y.o.)	NR
Toronto, Canada[J]	PM$_{10-2.5}$	1.128 (1.049, 1.213)	12.2 (max 68)
Total Cardiovascular:			
Atlanta, GA[K]	PM$_{10-2.5}$	1.176 (0.954, 1.450)	9.39 (±4.52)
Toronto, Canada[I]	PM$_{10-2.5}$	1.205 (1.082, 1.341)	11.6 (1, 56)
Ischemic Heart Disease:			
Detroit, MI[C]	PM$_{10-2.5}$	1.105 (1.027, 1.189	13 (4, 50)
Toronto, Canada[J]	PM$_{10-2.5}$	1.037 (1.013, 1.062))	12.2 (max 68)
Dysrhythmias:			
Detroit, MI[C]	PM$_{10-2.5}$	1.002 (0.877, 1.144)	13 (4, 50)
Atlanta, GA[K]	PM$_{10-2.5}$	1.532 (1.021, 2.30)	9.39 (±4.52)
Toronto, Canada[J]	PM$_{10-2.5}$	1.051 (0.998, 1.108)	12.2 (max 68)
Heart Failure:			
Detroit, MI[C]	PM$_{10-2.5}$	1.052 (0.967, 1.144)	13 (4, 50)
Toronto, Canada[J]	PM$_{10-2.5}$	1.079 (1.023, 1.138)	12.2 (max 68)
Stroke:			
Detroit, MI[C]	PM$_{10-2.5}$	1.049 (0.953, 1.155)	13 (4, 50)
Cerebrovascular:			
Toronto, Canada[J]	PM$_{10-2.5}$	"NEG" reported	12.2 (max 68)

TABLE 9-15 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES (PM$_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-μg/m^3 Increase	Reported PM Levels Mean (Min, Max)***
Peripheral Circulation Diseases:			
Toronto, Canada[J]	PM$_{10-2.5}$	1.056 (1.003, 1.112)	12.2 (max 68)
Asthma:			
Seattle, WA[L]	PM$_{10-2.5}$	1.111 (1.028, 1.201)	16.2 (6, 29)
Toronto, Canada[J]	PM$_{10-2.5}$	1.111 (1.058, 1.166)	12.2 (max 68)
Increased Respiratory Symptoms		Odds Ratio (95% CI) per 25-μg/m^3 PM Increase	
Six U.S. Cities[M] (Lower Respiratory Symptoms)	PM$_{10-2.5}$	1.51 (0.66, 3.43)	NR
Six U.S. Cities[M] (Cough)	PM$_{10-2.5}$	1.77 (1.24, 2.55)	NR
Southwest Virginia[N] (Runny or Stuffy Nose)	PM$_{10-2.5}$	2.62 (1.16, 5.87)	NR
Decreased Lung Function		PEFR change (L/min) per 25-μg/m^3 PM Increase	
Southwest Virginia[O]	PM$_{10-2.5}$	am PEFR 5.3 (2.6, 8.0)	27.07 (4.89, 69.07)
Uniontown, PA[M] (Reanalysis)	PM$_{10-2.5}$	pm PEFR +1.73 (5.67, -2.2)	NR
State College, PA[M] (Reanalysis)	PM$_{10-2.5}$	pm PEFR -0.28 (2.86, -3.45)	NR
Philadelphia, PA[P]	PM$_{10-2.5}$	am PEFR -4.31 (-11.44, 2.75)	9.5 (IQR 5.1)

* Studies highlighted in the 1996 CD are in italics; new studies in plain text. For purposes of comparison across studies, results of single-pollutant models are presented in these tables; co-pollutant model results are presented and discussed in more detail in Chapter 8.
** Relative Risk (95% Confidence Interval), except for Fairley (1999) and Lipfert et al. (2000), where insufficient data were available to calculate confidence intervals so p-value is given in parentheses.
*** Min, Max 24-h PM indicator level shown in parentheses unless otherwise noted as (±S.D.), NR = not reported, or R = range of values from min-max, no mean value reported.

References:

[A]Schwartz et al. (1996)   [G]Fairley (1999)   [M]Schwartz and Neas (2000)
[B]Ostro et al. (2000)   [H]Burnett et al. (2000)   [N]Naeher et al. (1999)
[C]Lippmann et al. (2000)   [I]Burnett et al. (1997)   [O]Zhang et al. (2000)
[D]Lipfert et al. (2000a)   [J]Burnett et al. (1999)   [P]Neas et al. (1999)
[E]Mar et al. (2000)   [K]Tolbert et al. (2000)   [Q]Moolgavkar (2000b)
[F]Smith et al. (2000)   [L]Sheppard et al. (1999)
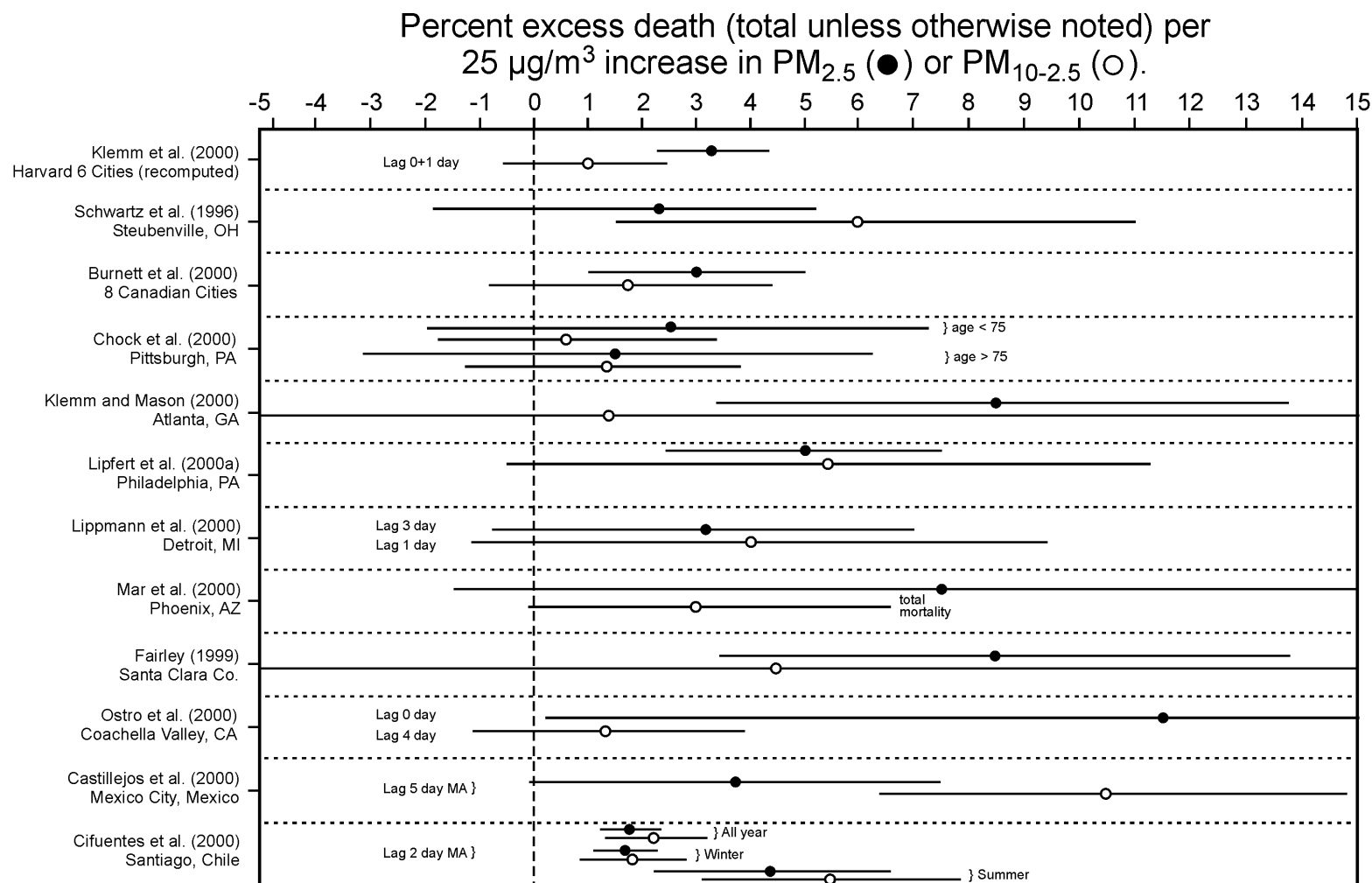
Figure 9-25. Percent excess risks estimated per 25-μg/m^3 increase in PM$_{2.5}$ or PM$_{10-2.5}$ from new studies evaluating both PM$_{2.5}$ and PM$_{10-2.5}$ data for multiple years. All lags = 1 day, unless indicated otherwise.

1   molds, endotoxins, etc.) to the observed coarse particle effects in at least some locations.

2   Overall, for U.S. and Canadian cities, effect size estimates for the coarse fraction ($PM_{10-2.5}$) of

3   those inhalable thoracic particles capable of depositing in TB and A regions of the respiratory

4   tract generally appear to fall in the range of 0.5 to 6.0% excess total (nonaccidental) deaths per

5   25 $\mu g/m^3$ of 24-h $PM_{10-2.5}$. Respective increases for cause-specific mortality are 3.0 to 8.0% for

6   cardiovascular and 3.0 to 16.0% for respiratory causes per 25-$\mu g/m^3$ increase in 24-h $PM_{10-2.5}$.

7

8   **Chemical Components of Particulate Matter.** Several new studies examined the role of

9   specific chemical components of PM in relation to mortality risks. Studies of U.S. and Canadian

10   cities showed mortality associations with one or more of several specific fine particle

11   components of PM, including H^+, sulfate, nitrate, as well as COH; but their relative importance

12   varied from city to city, likely depending, in part, on their concentrations (e.g., no clear

13   associations in those cities where H^+ and sulfate levels were very low [i.e., circa nondetection

14   limits]). Figure 9-26 depicts relatively consistent estimates of total mortality excess risk

15   resulting from a 5-$\mu g/m^3$ increase in sulfate, possibly reflecting impacts of sulfate per se or

16   perhaps sulfate serving as a surrogate for fine particles in general. Sulfate effect size estimates

17   generally fall in the range of 1 to 4% excess total mortality per 5-$\mu g/m^3$ increase for U.S. and

18   Canadian cities.

19   A significant factor in some western cities is the occasional occurrence of high levels of

20   windblown crustal particles that constitute the major part of the coarse PM fraction and a

21   substantial fraction of intermodal fine particles ($PM_{2.5-1}$). The small-size tail of the windblown

22   crustal particles extends into the $PM_{2.5-1}$ size range (intermodal), at times contributing

23   significantly to $PM_{2.5}$. Claiborn et al. (2000) report that in Spokane, WA, $PM_{2.5}$ constitutes about

24   30% of PM_{10} on dust event days, but 48% on days preceding the dust event. The intermodal

25   fraction represents about 51% of $PM_{2.5}$ during windblown dust events, about 28% on preceding

26   days. However, PM_1 in Spokane often shows little change during dust events, when coarse

27   particles (presumably crustal particles) are transported into the region. The lack of increased

28   mortality during periods of time with high wind speeds and presumably high crustal material

29   concentrations was shown by Schwartz et al. (1999) for Spokane, and by Pope et al. (1999b) for

30   three cities in the Wasatch front region of Utah. Other recent studies suggest that coarse

31   particles, as well as fine particles, may be associated with excess mortality in certain U.S.

Percent excess death (total mortality, unless otherwise noted) per 5 μg/m³ increase in sulfate
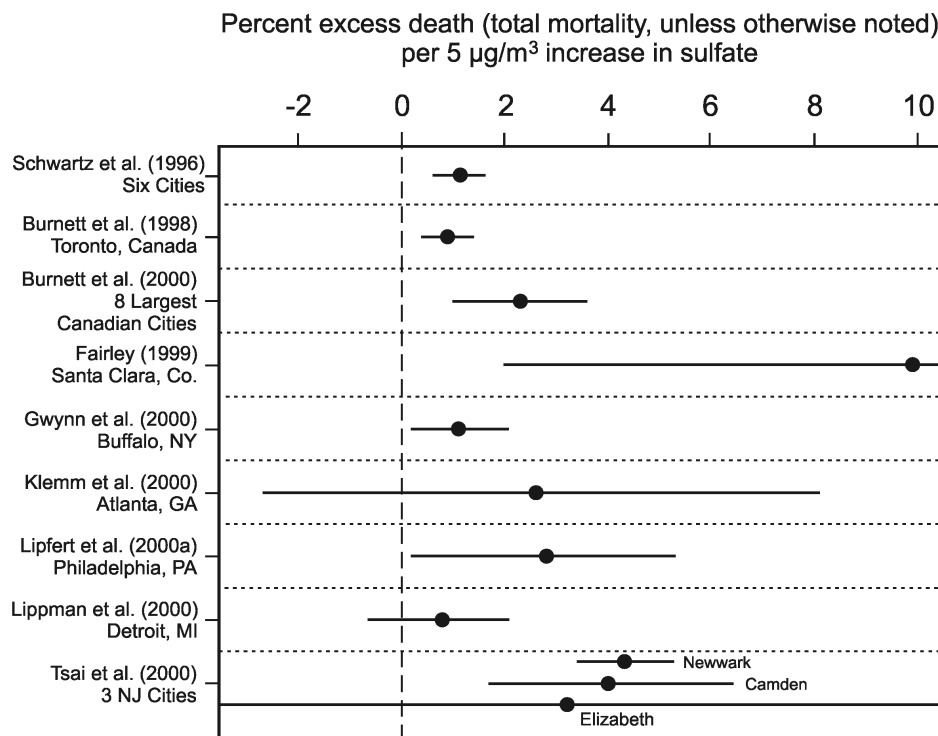
Figure 9-26. Relative risks estimated per 5-μg/m^3 increase in sulfate from U.S. and Canadian studies in which both PM$_{2.5}$ and PM$_{10-2.5}$ data were available.

1 locations e.g., in Phoenix, AZ (Smith et al., 2000; Clyde et al., 2000; Mar et al., 2000) the

2 Coachella Valley of California (Ostro et al., 2000), Mexico City (Castillejos et al., 2000) or

3 Santiago, Chile (Cifuentes et al., 2000). However, the coarse particle association with mortality

4 may not be caused by the crustal components. An important advantage of using source profiles

5 for PM$_{2.5}$ in western cities is that it allows separation of crustal PM from accumulation-mode PM

6 derived from anthropogenic origins.

7   Several new studies highlighted in Chapter 8 conducted source-category-oriented

8 evaluations of PM components using factor analysis (see Table 9-16). The results of these

9 studies (Laden et al., 2000; Mar et al., 2000; Tsai et al., 2000; Özkaynak et al., 1996) generally

10 suggest that a number of combustion-related source-categories are associated with excess

11 mortality risk, including: regional sulfate; automobile emissions; coal combustion; oil burning;

12 and vegetative (biomass) burning. In contrast, the crustal factor from fine particles was generally

TABLE 9-16. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PARTICULATE MATTER COMPONENTS IN RECENT STUDIES

Author, City	Source Categories and Species with High Factor Loadings Used to Suggest the Source Categories	Source Categories Associated with Mortality. Comments.
Laden et. al., (2000) Harvard Six Cities 1979-1988	Soil and crustal material: Si Motor vehicle emissions: Pb Coal combustion (Regional Sulfate): Se, S Fuel oil combustion: V Salt: Cl Note: the trace elements are from $PM_{2.5}$ samples	The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000). Phoenix, AZ 1995-1997	*$PM_{2.5}$ (from DFPSS) trace elements:* Motor vehicle emissions and resuspended road dust: Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 Soil: Al, Si, and Fe Vegetative burning: OC and K_S (soil-corrected potassium) Local SO_2 sources: SO_2 Regional sulfate: S --- *$PM_{10-2.5}$ (from dichot) trace elements:* Soil: Al, Si, K, Ca, Mn, Fe, Sr, and Rb A source of coarse fraction metals: Zn, Pb, and Cu A marine influence: Cl	$PM_{2.5}$ factors results: Soil factor and local SO_2 factor were negatively associated with total mortality. Regional sulfate was positively associated with total mortality on the same day, but negatively associated on the lag 3 day. Motor vehicle factor, vegetative burning factor, and regional sulfate factor were significantly positively associated with cardiovascular mortality. Factors from dichot $PM_{10-2.5}$ trace elements were not analyzed for their associations with mortality because of the small sample size (every-third-day samples from June 1996).
Özkaynak et al. (1996). Toronto, Canada.	Motor vehicle emissions: CO, COH, and NO_2	Motor vehicle factor was a significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	Motor vehicle emissions: Pb and CO Geological (Soil): Mn and Fe Oil burning: V and Ni Industrial: Zn, Cu, and Cd (separately) Sulfate/secondary aerosol: Sulfate Note: The trace elements are from PM_{15} samples.	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.

1   not positively associated with total mortality, with Mar et al. (2000) reporting a negative

2   association between the crustal component of $PM_{2.5}$ and cardiovascular mortality.

3   However, these source-category-oriented evaluation results are derived from relatively

4   limited underlying analytic bases for resolving source categories and the identification of souce

1   categories must be viewed with caution at this time. For example, whereas Laden et al. (2000)

2   had 6211 days of every-other-day data from the Harvard Six City Study of eastern/midwest U.S.

3   cities, they had only elements in $PM_{2.5}$ analyzed by X-ray fluorescence (XRF) spectroscopy (no

4   organic PM or gases). They used factors in the regression analysis and used Pb as a tracer to

5   identify a motor vehicle source category, Se to identify a coal combustion source category, and Si

6   as a tracer for soil. Since the "coal combustion" factor had a high loading of S as well as Se, it

7   could equally as well have been identified as the regional sulfate source category. The "motor

8   vehicle" and "coal combustion" sources were statistically significant for total mortality as well as

9   mortality resulting from ischemic heart disease and respiratory diseases (COPD plus pneumonia).

10   The crustal component had a negative association with total mortality.

11   The Mar et al. (2000) study had 3 years of pollutant data for Phoenix, AZ. In addition to

12   elements determined by XRF, they had pollutant gases (CO, NO_2, SO_2, and O_3) and total,

13   organic, and elemental carbon. They were able to identify five factors and attributed them to five

14   source categories. Motor vehicles (plus resuspended road dust), vegetative burning, and regional

15   sulfate all had statistically significant associations with cardiovascular mortality, but soil

16   (indexed by Si and Al, as crustal markers) had a statistically significant negative association.

17   Also of importance, Mar et al. (2000) found significant associations between cardiovascular

18   mortality and $PM_{2.5}$ and marginally significant ($p < 0.10$) associations between total mortality and

19   $PM_{10-2.5}$.

20   Tsai et al. (2000) had only 156 days of data and used measurements of CO, sulfate, and

21   some elements; and they did not have Si, Ca, Al, or Mg as soil tracers nor Se as a tracer of coal

22   combustion, although much of the sulfate probably came from coal combustion. They had three

23   fractions of extractable organic matter, but these did not appear to be useful in determining

24   factors. Statistically significant ($p > 0.05$) factors for both total daily deaths and combined

25   cardiovascular and respiratory daily deaths in at least one or another of the three New Jersey

26   cities studied (Newark, Camden, and Elizabeth) were attributed to motor vehicles, oil burning,

27   and sulfate. Also, an industrial source containing Zn and Cd was statistically significant for total

28   deaths in Newark; and an industrial source containing Cd was marginally statistically significant

29   for cardiorespiratory disease in Elizabeth.

1   Özkaynak et al. (1996) had only TSP, coefficient of haze (COH), and gases; however, they

2   reported that a factor with COH, CO, and NO_2 (considered to be representative of motor vehicle

3   emissions) was associated with mortality in Toronto, Canada.

4   None of these studies had measurements of nitrate or semivolatile organic compounds nor

5   did they use the newest, and most effective, techniques for source apportionment. For example,

6   using positive matrix factorization, Ramadan et al. (2000) were able to determine eight factors

7   using the same data set as Mar et al. (2000). In spite of these deficiencies, all four studies were

8   able to associate one or more types of mortality with motor vehicles, several with coal

9   combustion, and three with sulfate.

10   Factor analyses also were described briefly in a report by Lippmann et al. (2000). In that

11   study, neither sulfate nor acid aerosols were related significantly to morbidity or mortality, but

12   the concentrations were extremely low (with about 70% of the acid measurements below

13   detection limit).

14   It is difficult to compare these source-categories-related assessments. They are based on

15   different regions of the country over different periods of time when the sources of particles,

16   marker elements such as Pb, and other urban air pollutants were changing greatly. Also, each of

17   these studies constructed factors based on city-specific data. Thus, the factors in each study are

18   based on the idiosyncrasies of the specific data set for each city in the study, so the factors may

19   indeed represent different sources in different locations. Nevertheless, although somewhat

20   limited at this time, the new factor analysis results appear to implicate ambient PM derived from

21   fossil fuel (oil, coal) combustion and vegetative burning, as well as secondarily formed sulfates,

22   as important contributors to observed mortality effects, but not crustal particles.

23   In summary, the new evidence suggests that exposure to particles from several different

24   source categories, and of different composition and size, may have independent associations with

25   health outcomes. The excess risks from different types of combustion sources (coal, oil,

26   gasoline, wood, and vegetation) may vary from place to place and from time to time, so that

27   substantial intra-regional and inter-regional heterogeneity would be expected. Likewise,

28   although earlier evaluations in the 1996 PM AQCD seemed to indicate coarse particles and

29   intermodal particles of crustal composition as not likely being associated with adverse health

30   effects, there are now some reasonably credible studies suggesting that coarse particles (although

31   not necessarily those of crustal composition) may be associated with excess mortality in at least

1   some locations. These notably include areas where past deposition of fine PM metals from

2   smelter (Phoenix) or steel mills (Steubenville) onto surrounding soils may result in enhanced

3   toxicity of later resuspended coarse ($PM_{10-2.5}$) particles.

4

Updated Epidemiologic Findings for Long-Term Particulate Matter Exposure
Effects on Mortality

7   The 1996 PM AQCD indicated that past epidemiologic studies of chronic PM exposures

8   collectively indicate increases in mortality to be associated with long-term exposure to airborne

9   particles of ambient origins (see appendix Table 9A-3). The PM effect size estimates for total

10   mortality from these studies also indicated that a substantial portion of these deaths reflected

11   cumulative PM impacts above and beyond those exerted by acute exposure events. Table 9-17

12   shows long-term exposure effects estimates (RR values) per variable increments in ambient PM

13   indicators in U.S. and Canadian cities, including results from newer analyses since the 1996 PM

14   AQCD.

15   One of the most important advances since the 1996 PM AQCD is the substantial

16   verification and extension of the findings of the Six City prospective cohort study (Dockery

17   et al., 1993) and the cohort study relating American Cancer Society (ACS) health data to

18   fine-particle data from 50 cities and sulfate data from 151 cities (Pope et al., 1995). The

19   reanalyses, sponsored by the Health Effects Institute (HEI), included a data audit, replication of

20   the original investigators' findings, and additional analyses to explore the sensitivity of the

21   original findings to other model specifications. The investigators of the HEI Reanalysis Project

22   (Krewski et al., 2000) first performed a data audit, using random samples to verify the accuracy

23   of the data sets used in the original Six City analyses, including death certificate data, air

24   pollution data, and socioeconomic data. In general, the air pollution data were reproducible and

25   correlated highly with the original aerometric data in Pope et al. (1995).

26   The reanalyses substantially verified the findings of the original investigators, with $PM_{2.5}$ or

27   sulfate relative risk (RR) estimates for total mortality and for cardiopulmonary mortality differing

28   at most by ±0.02 (±2% excess risk) from the least polluted to the most polluted cities in the

29   study. A larger difference was noted for the $PM_{2.5}$ lung cancer relative risk in the Six Cities

30   study, 1.37 originally and 1.43 in the reanalysis, neither estimate being statistically significant.

31   The sensitivity analyses for the Six Cities study found generally similar results with other

TABLE 9-17. EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Increased Total Mortality in Adults		Relative Risk (95% CI)	
Six City[B]	*$PM_{15/10}$ (20 $\mu g/m^3$)*	*1.18 (1.06-1.32)*	*18-47*
	$PM_{2.5}$ (10 $\mu g/m^3$)	*1.13 (1.04-1.23)*	*11-30*
	$SO_4^=$ (15 $\mu g/m^3$)	*1.46 (1.16-2.16)*	*5-13*
ACS Study[C] (151 U.S. SMSA)	*$PM_{2.5}$ (10 $\mu g/m^3$)*	*1.07 (1.04-1.10)*	*9-34*
	$SO_4^=$ (15 $\mu g/m^3$)	*1.10 (1.06-1.16)*	*4-24*
Six City Reanalysis[D]	$PM_{15/10}$ (20 $\mu g/m^3$)	1.19 (1.06-1.34)	18.2-46.5
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.13 (1.04-1.23)	11.0-29.6
ACS Study Reanalysis[D]	$PM_{15/10}$ (20 $\mu g/m^3$) (SSI)	1.02 (0.99-1.04)	58.7 (34-101)
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.07 (1.04-1.10)	9.0-33.4
ACS Study Extended Analyses[Q]	$PM_{2.5}$ (10 $\mu g/m^3$)	1.04 (1.01-1.08)	21.1 (SD=4.6)
Southern California[E]	PM_{10} (50 $\mu g/m^3$)	1.242 (0.955-1.616) (males)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	1.082 (1.008-1.162) (males)	
	PM_{10} (50 $\mu g/m^3$)	0.879 (0.713-1.085) (females)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	0.958 (0.899-1.021) (females)	
Increased Bronchitis in Children		Odds Ratio (95% CI)	
Six City[F]	*TSP (50 $\mu g/m^3$)*	*3.26 (1.13, 10.28)*	*20-59*
Six City[G]	*TSP (100 $\mu g/m^3$)*	*2.80 (1.17, 7.03)*	*39-114*
24 City[H]	*H^+ (100 $nmol/m^3$)*	*2.65 (1.22, 5.74)*	*6.2-41.0*
24 City[H]	*$SO_4^=$ (15 $\mu g/m^3$)*	*3.02 (1.28, 7.03)*	*18.1-67.3*
24 City[H]	*$PM_{2.1}$ (25 $\mu g/m^3$)*	*1.97 (0.85, 4.51)*	*9.1-17.3*
24 City[H]	*PM_{10} (50 $\mu g/m^3$)*	*3.29 (0.81, 13.62)*	*22.0-28.6*
Southern California[I]	*$SO_4^=$ (15 $\mu g/m^3$)*	*1.39 (0.99, 1.92)*	*—*
12 Southern California communities[J] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	0.94 (0.74, 1.19) 1.16 (0.79, 1.68)	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[K] (children with asthma)	PM_{10} (19 $\mu g/m^3$) $PM_{2.5}$ (15 $\mu g/m^3$) Acid vapor (1.8 ppb)	1.4 (1.1, 1.8) 1.4 (0.9, 2.3) 1.1 (0.7, 1.6)	13.0-70.7 6.7-31.5 1.0-5.0 ppb

TABLE 9-17 (cont'd). EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Increased Cough in Children		Odds Ratio (95% CI)	
12 Southern California communities[J] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	1.06 (0.93, 1.21) 1.13 (0.92, 1.38)	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[K] (children with asthma)	PM_{10} (19 $\mu g/m^3$) $PM_{2.5}$ (15 $\mu g/m^3$) Acid vapor (1.8 ppb)	1.1 (0.0.8, 1.7) 1.3 (0.7, 2.4) 1.4 (0.9, 2.1)	13.0-70.7 6.7-31.5 1.0-5.0 ppb
Increased Obstruction in Adults			
Southern California[L]	PM_{10} (cutoff of 42 days/year >100 $\mu g/m^3$)	1.09 (0.92, 1.30)	NR
Decreased Lung Function in Children			
Six City[F]	*$PM_{15/10}$ (50 $\mu g/m^3$)*	*NS Changes*	*20-59*
Six City[G]	*TSP (100 $\mu g/m^3$)*	*NS Changes*	*39-114*
24 City[M]	*H^+ (52 nmoles/m^3)*	*−3.45% (-4.87, -2.01) FVC*	*6.2-41.0*
24 City[M]	*$PM_{2.1}$ (15 $\mu g/m^3$)*	*−3.21% (-4.98, -1.41) FVC*	*18.1-67.3*
24 City[M]	*$SO_4^=$ (7 $\mu g/m^3$)*	*−3.06% (-4.50, -1.60) FVC*	*9.1-17.3*
24 City[M]	*PM_{10} (17 $\mu g/m^3$)*	*−2.42% (-4.30, -.0.51) FVC*	*22.0-28.6*
12 Southern California communities[N] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	-24.9 (-47.2, -2.6) FVC -24.9 (-65.08, 15.28) FVC	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[N] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	-32.0 (-58.9, -5.1) MMEF -7.9 (-60.43, 44.63) MMEF	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[O] (4th grade cohort)	PM_{10} (51.5 $\mu g/m^3$) $PM_{2.5}$ (25.9 $\mu g/m^3$) $PM_{10-2.5}$ (25.6 $\mu g/m^3$) Acid vapor (4.3 ppb)	-0.58 (-1.14, -0.02) FVC growth -0.47 (-0.94, 0.01) FVC growth -0.57 (-1.20, 0.06) FVC growth -0.57 (-1.06, -0.07) FVC growth	NR
12 Southern California communities[O] (4th grade cohort)	PM_{10} (51.5 $\mu g/m^3$) $PM_{2.5}$ (25.9 $\mu g/m^3$) $PM_{10-2.5}$ (25.6 $\mu g/m^3$) Acid vapor (4.3 ppb)	-1.32 (-2.43, -0.20) MMEF growth -1.03 (-1.95, -0.09) MMEF growth -1.37 (-2.57, -0.15) MMEF growth -1.03 (-2.09, 0.05) MMEF growth	NR

TABLE 9-17 (cont'd). EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Decreased Lung Function in Adults			
Southern California[P] (% predicted FEV_1, females)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	+0.9 % (-0.8, 2.5) FEV_1	52.7 (21.3, 80.6)
Southern California[P] (% predicted FEV_1, males)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	+0.3 % (-2.2, 2.8) FEV_1	54.1 (20.0, 80.6)
Southern California[P] (% predicted FEV_1, males whose parents had asthma, bronchitis, emphysema)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	-7.2 % (-11.5, -2.7) FEV_1	54.1 (20.0, 80.6)
Southern California[P] (% predicted FEV_1, females)	SO_4^- (1.6 $\mu g/m^3$)	Not reported	7.4 (2.7, 10.1)
Southern California[P] (% predicted FEV_1, males)	SO_4^- (1.6 $\mu g/m^3$)	-1.5 % (-2.9, -0.1) FEV_1	7.3 (2.0, 10.1)

*Range of mean PM levels given unless, as indicated, studies reported overall study mean (min, max), or mean (±SD); NR=not reported.

[A]Results calculated using PM increment between the high and low levels in cities, or other PM increments given in parentheses; NS Changes = No significant changes.

References:
[B]Dockery et al. (1993)
[C]Pope et al. (1995)
[D]Krewski et al. (2000)
[E]Abbey et al. (1999)
[F]Dockery et al. (1989)
[G]Ware et al. (1986)
[H]Dockery et al. (1996)
[I]Abbey et al. (1995a,b,c)
[J]Peters et al. (1999b)
[K]McConnell et al. (1999)
[L]Berglund et al. (1999)
[M]Raizenne et al. (1996)
[N]Peters et al. (1999a)
[O]Gauderman et al. (2000)
[P]Abbey et al. (1998)
[Q]Pope et al. (2002)

1   individual covariates included. The time-dependent covariate model for total mortality (taking

2   into account higher postexposures in early years of the study and changes over time to the last

3   years of the study) had a substantially lower RR than the model without time-dependent

4   covariates. Educational level made a large difference, with individuals having less than a high

5   school education at much greater risk for mortality than those with any postsecondary education.

1   Among the ecological covariates, sulfates adjusted for artifact had little effect on the risk

2   estimates for total mortality compared to that without adjustment, but, in the ACS study, the filter

3   adjustment actually increased the relative risk for all causes and cardiopulmonary mortality,

4   while substantially reducing the estimated sulfate effect on lung cancer. Inclusion of SO_2 as an

5   additional ecological covariate greatly reduced the estimated $PM_{2.5}$ and sulfate effects in the ACS

6   study, whereas a spatial model including SO_2 effects caused only a modest reduction of the

7   estimated $PM_{2.5}$ and sulfate effects. However, the SO_2 effects were reduced greatly when sulfates

8   were included in the model. Sulfur dioxide and sulfates often are highly correlated, because of

9   the formation of secondary sulfates.

10   Many model selection issues in the prospective cohort studies are analogous to those in the

11   time series analyses. One issue of particular concern is whether the exposure indices used in the

12   analyses adequately characterize the exposure of the participants in the study during the months

13   or years preceding death. This question is particularly conspicuous in regard to the Pope et al.

14   (1995) study, in which $PM_{2.5}$ and sulfate data were collected in the 1979 to 1982 period from the

15   EPA AIRS database and the Inhalable Particle Network, largely preceding the collection of the

16   ACS cohort data by only a few years, and so possibly not adequately reflecting exposure to

17   presumably much higher PM concentrations occurring long before the cohort was recruited, nor

18   exposure to presumably lower concentrations during the study. This issue was raised in the 1996

19   PM AQCD. However, the Six Cities Study did have air pollution data and repeated survey data

20   over time, with $PM_{2.5}$ and sulfate data measured every other day and sometimes daily, and so the

21   new investigators were able to use the information about time-dependent cumulative PM

22   concentrations during the course of the study. Changes in smoking status and body mass index

23   over the 10 to12 years of the study had little effect on risk estimates, but taking into account the

24   decrease in particle concentrations from the earlier years to the later years reduced the effect size

25   estimate substantially, although it remained statistically significant. Nevertheless, overall, the

26   reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) "replicated the

27   original results, and tested those results against alternative risk models and analytic approaches

28   without substantively altering the original findings of an association between indicators of

29   particulate matter air pollution and mortality."

30   The shape of the relationship of concentration to mortality also was explored. Preliminary

31   findings suggest some possible nonlinearity, but further study is needed. Among the most

1   important new findings of the study are spatial relationships between mortality and air pollution,

2   discussed later below.

3   Recently reported extension of the ACS analyses (Pope et al., 2002) to include additional

4   years of data provides further substantiation of originally reported findings for total, respiratory,

5   and cardiovascular mortality. Also of great importance, these new analyses provide much

6   stronger evidence substantiating links between long-term ambient fine PM exposures and lung

7   cancer. This is consistent with findings of increased lung cancer risk being associated with

8   exposure with diesel exhaust particles, an important constituent of $PM_{2.5}$ in many U.S. urban

9   areas.

10   With regard to the role of various PM constituents in the PM-mortality association, past

11   cross-sectional studies generally have found that the fine particle component, as indicated either

12   by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with chronic PM

13   exposure-mortality. Although the relative measurement errors of the various PM constituents

14   must be further evaluated as a possible source of bias in these estimate comparisons, the Harvard

15   Six-Cities study and the latest reported AHSMOG prospective semi-individual study results

16   (Abbey, et al., 1999; McDonnell et al., 2000) are both indicative of the fine mass components of

17   PM likely being associated more strongly with the mortality effects of PM than coarse PM

18   components. The ACS study, its reanalyses, and its recent extension all further substantiate

19   ambient fine particle effects, including increased risk not only of cardiopulmonary-related

20   mortality but lung cancer mortality as well.

21   Several other new studies report epidemiologic evidence indicating that: (a) PM exposure

22   early in pregnancy (during the first month) may be associated with slowed intrauterine growth

23   leading to low birth weight events (Dejmek et al., 1999); and (b) early postnatal PM exposures

24   may lead to increased infant mortality (Woodruff et al., 1997; Boback and Leon, 1999; Loomis

25   et al., 1999; Lipfert et al., 2000b).

26

27   **9.12.2.2 Relationships of Ambient Particulate Matter Concentrations to**
28   **   Morbidity Outcomes**

29   New epidemiology studies add greatly to the overall database relating morbidity outcomes

30   to ambient PM levels. These include much additional evidence for cardiovascular and

31   respiratory diseases being related to ambient PM. The newer epidemiology studies expand the

1   evidence on cardiovascular (CVD) disease and are discussed first below, followed by discussion

2   of respiratory disease effects with particular emphasis on newly enhanced evidence for

3   PM-asthma relationships.

4

5   *Cardiovascular Effects of Ambient Particulate Matter Exposures*

6   About 75% of all U.S. deaths occur in persons at least 65 years old, and, of these, nearly

7   40% are for cardiac causes (nearly 45%, if deaths from cerebrovascular causes are also included).

8   Thus, if ambient PM exposure indeed produces increased total mortality in the elderly, it would

9   seem possible that cardiovascular (CVD) deaths may be involved.

10

11   **Cardiovascular Hospital Admissions.** Just two studies were available for review in the 1996

12   PM AQCD that provided data on acute cardiovascular morbidity outcomes (Schwartz and

13   Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time series design using

14   standard statistical methods. Analyzing 4 years of data on the $\geq$65-year-old Medicare population

15   in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic

16   heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an

17   analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett and

18   colleagues (1995) reported significant associations between particle sulfate concentrations, as

19   well as other air pollutants, and daily cardiovascular admissions. The relative risk because of

20   sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions.

21   The 1996 PM AQCD concluded on the basis of these studies that, "There is a suggestion of a

22   relationship to heart disease, but the results are based on only two studies and the estimated

23   effects are smaller than those for other endpoints." The PM AQCD went on to state that acute

24   impacts on CVD admissions had been demonstrated for elderly populations (i.e., $\geq$65), but that

25   insufficient data existed to assess relative impacts on younger populations.

26   Although the literature still remains relatively sparse, an important new body of data now

27   exists that both extends the available quantitative information on relationships between ambient

28   PM pollution and hospital CVD admissions, and that, more intriguingly, illuminates some of the

29   physiological changes that may occur on the mechanistic pathway leading from PM exposure to

30   adverse cardiac outcomes. Figure 9-27 depicts excess risk estimates derived from 10 studies of

31   acute PM_{10} exposure effects on CVD admissions in U.S. cities. Although new studies depicted
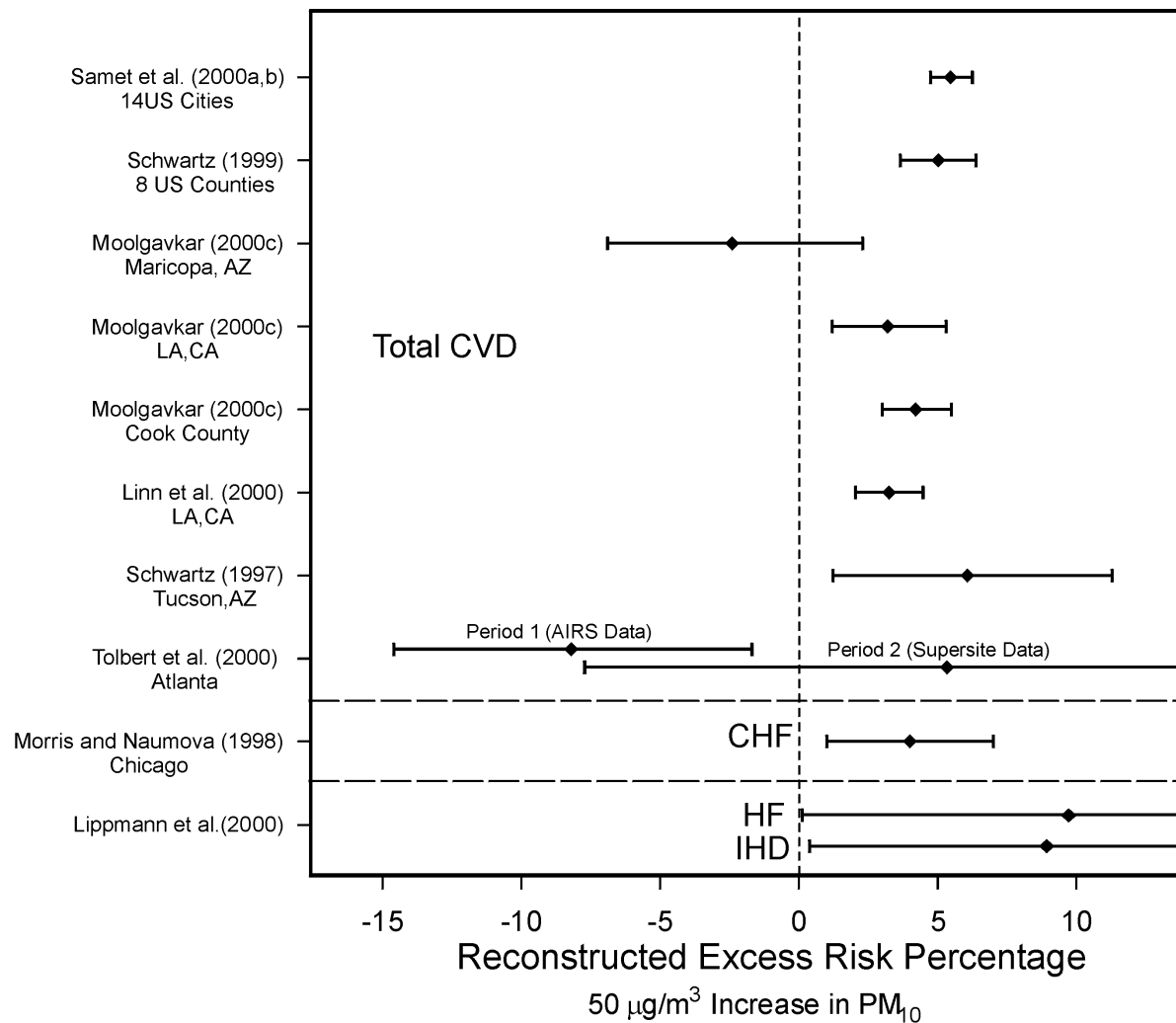
Figure 9-27. Acute cardiovascular hospitalizations and PM exposure excess risk estimates derived from selected U.S. PM$_{10}$ studies. CVD = cardiovascular disease and CHF = congestive heart failure.

1 in Figure 9-27 have reported generally consistent associations between daily hospitalizations for

2 cardiovascular disease and measures of PM, the data not only implicate PM, but also CO and

3 NO$_2$ as well, possibly because of covarying of PM and these other gaseous pollutants derived

4 from common emission sources (e.g., motor vehicles). Taken as a whole, this body of evidence

5 suggests that PM is likely an important risk factor for cardiovascular hospitalizations in the

6 United States.

1   For example, in the recently published NMMAPS 14-city analysis of daily CVD hospital

2   admissions in persons 65 and older in relation to PM_{10} (Samet et al., 2000a,b). The mean risk

3   estimate (for average 0-1 day lag) was a 8.5% increase in CVD admissions per 50 μg/m^3 PM_{10}

4   (95% CI: 1.0 to 33.0%). No relationship was observed between city-specific risk estimates and

5   measures of socioeconomic status, including percent living in poverty, percent non-white, and

6   percent with college educations. In another study, remarkably consistent PM_{10} associations with

7   cardiovascular admissions were observed across eight U.S. metropolitan areas, with a 25 μg/m^3

8   increase in PM_{10} associated with between 1.8 and 4.2 percent increases in admissions (Schwartz,

9   1999). Also, in a study of Los Angeles data from 1992-1995, PM_{10}, CO, and NO_2 were all

10   significantly associated with increased cardiovascular admission in single-pollutant models

11   among persons 30 and older (Linn et al., 2000). Moolgavkar (2000c) analyzed PM_{10}, CO, NO_2,

12   O_3, and SO_2 in relation to daily total cardiovascular (CVD) and total cerebrovascular admissions

13   for persons 65 and older from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ),

14   and found that, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) was associated with CVD

15   admissions in Cook and LA counties but not in Maricopa county. On the other hand, in

16   two-pollutant models in Cook and LA counties, the PM risk estimates diminished and/or were

17   rendered nonsignificant.

18   The recent NMMAPS study of PM_{10} concentrations and hospital admissions by persons

19   65 and older in 14 U.S. cities provides particularly important findings of positive and significant

20   associations, even when concentrations are below 50 μg/m^3 (Samet et al., 2000a,b). As noted in

21   Table 9-18, this study indicates PM_{10} effects similar to other cities, but with narrower confidence

22   bands, because of its greater power derived by combining multiple cities in the same analysis.

23   This allows significant associations to be identified, despite the fact that many of the cities

24   considered have relatively small populations and that each of the 14 cities had mean PM_{10} below

25   50 μg/m^3.

26

27   **Physiologic Measures of Cardiac Function.** Several very recent studies by independent groups

28   of investigators have also reported longitudinal associations between ambient PM concentrations

29   and physiologic measures of cardiovascular function. These studies measure outcomes and most

30   covariates at the individual level, making it possible to draw conclusions regarding individual

31   risks, as well as to explore mechanistic hypotheses. For example, several studies recently have

TABLE 9-18. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-μg/m^3 INCREASE IN 24-HOUR PM$_{10}$ IN 14 U.S. CITIES

	CVD		COPD		Pneumonia	
	% Increase	(95% CI)	% Increase	(95% CI)	% Increase	(95% CI)
Constrained Lag Models (Fixed Effect Estimates)						
One-day mean[a]	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Previous-day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Two-day mean[b]	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
PM$_{10}$ <50 μg.m^3 (2-day mean)[b]	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Unconstrained Distributed Lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.90	(1.46, 2.34)
Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)

[a]Lag.
[b]Mean of lag 0 and lag 1.

Source: Samet et al. (2000a,b).

1 reported temporal associations between PM exposures and various electrocardiogram (ECG)

2 measures of heart beat or rhythm in panels of elderly subjects. Reduced HR variability is a

3 predictor of increased cardiovascular morbidity and mortality risks. Three independent studies

4 reported decreases in HR variability associated with PM in elderly cohorts, although r-MSSD

5 (one measure of high-frequency HR variability) showed elevations with PM in one study.

6   Differences in methods used and results obtained across the studies argue for caution in

7 drawing any strong conclusions yet regarding PM effects from them, especially in light of the

8 complex intercorrelations that exist among measures of cardiac physiology, meteorology, and air

9 pollution (Dockery et al., 1999). Still, the new heart rhythm results, in general, comport well

10 with other findings of cardiovascular mortality and morbidity endpoints being associated with

11 ambient PM. Chapter 5 discusses available exposure studies of elderly subjects with CVD, such

12 as the Sarnat et al. (2000) Baltimore study. Less active groups tend to have lower exposure to

13 nonambient PM because of reduced personal activity. However, Williams et al. (2000a,b,c)

1   report a very high pooled correlation coefficient between $PM_{2.5}$ personal exposure and outdoor

2   concentrations. These exposure studies tend to enhance the plausibility of panel study findings

3   of impacts on HR variability being caused by exposure to ambient-generated PM.

4

5   **Changes in Blood Characteristics.** Additional epidemiologic findings (Peters et al., 1997a)

6   also provide new evidence for ambient PM exposure effects on blood characteristics (e.g.,

7   increased c-reactive protein in blood) thought to be associated with increased risk of serious

8   cardiac outcomes (e.g., heart attacks).

9

10   *Key Conclusions Regarding PM-CVD Morbidity*

11   Overall, the newly available studies of PM-CVD relationships appear to support the

12   following conclusions regarding several key issues:

13

14   <u>Temporal Patterns of Response</u>. The evidence from recent time series studies of CVD

15   admissions suggests rather strongly that PM effects are likely maximal at lag 0, with some

16   carryover to lag 1.

17

18   <u>Physical and Chemical Attributes Related to Particulate Matter Health Effects</u>. The

19   characterization of ambient PM attributes associated with acute CVD is incomplete. Insufficient

20   data exist from the time series CVD hospital admissions literature or from the emerging

21   individual-level studies to provide clear guidance as to which PM attributes, defined either on the

22   basis of size or composition, determine potency. The epidemiologic studies published to date

23   have been constrained by the limited availability of multiple PM metrics. Where multiple PM

24   metrics exist, they often are of differential quality because of differences in numbers of

25   monitoring sites and in monitoring frequency. Until more extensive and consistent data become

26   available for epidemiologic research, the question of PM size and composition, as they relate to

27   acute CVD impacts, will remain open.

28

29   <u>Susceptible Subpopulations</u>. Because they lack data on individual subject characteristics,

30   ecologic time series studies provide only limited information on susceptibility factors based on

31   stratified analyses. The relative impact of PM on cardiovascular (and respiratory) admissions

1   reported in ecologic time series studies is generally somewhat higher than those reported for total

2   admissions. This provides some limited support for the hypothesis that acute effects of PM

3   operate via cardiopulmonary pathways or that persons with preexisting cardiopulmonary disease

4   have greater susceptibility to PM, or both. Although there is some data from the ecologic time

5   series studies showing larger relative impacts of PM on cardiovascular admissions in adults 65

6   and over as compared with younger populations, the differences are neither striking nor

7   consistent. Some individual-level studies of cardiophysiologic function suggest that elderly

8   persons with preexisting cardiopulmonary disease are susceptible to subtle changes in heart rate

9   variability (HRV) in association with PM exposures. However, because younger and healthier

10   populations have not yet been assessed, it is not possible to say at present whether the elderly

11   have clearly increased susceptibility compared to other groups, as indexed by cardiac

12   pathophysiological indices such as HRV.

13

14   <u>Role of Other Environmental Factors</u>. The ecologic time series morbidity studies published since

15   1996 generally have controlled adequately for weather influences. Thus, it is unlikely that

16   residual confounding by weather accounts for the PM associations observed. With one possible

17   exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed

18   extensively as yet in the individual-level studies of cardiac physiologic function. Thus, the

19   possibility of confounding in such studies as yet cannot be discounted totally or readily.

20   Co-pollutants have been analyzed rather extensively in many of the recent time series studies of

21   hospital admissions and PM. In some studies, PM clearly carries an independent association

22   after controlling for gaseous co-pollutants. In others, the "PM effects" are reduced markedly

23   once co-pollutants are added to the model. Among the gaseous criteria pollutants, CO has

24   emerged as the most consistently associated with cardiovascular (CVD) hospitalizations. The

25   CO effects are generally robust in the multi-pollutant model, sometimes as much so as PM

26   effects. However, the typically low levels of ambient CO concentrations in most such studies

27   and minimal expected impacts on carboxyhemoglobin levels and consequent associated hypoxic

28   effects thought to underlie CO CVD effects complicate interpretation of the CO findings and

29   argue for the possibility that CO may be serving as a general surrogate for combustion products

30   (e.g., PM) in the ambient pollution mix. See the most recent EPA CO Criteria Document (U.S.

31   Environmental Protection Agency, 2000a).

1   *Respiratory Effects of Ambient Particulate Matter Exposures*

2   The number of studies examining hospitalization and emergency department visits for

3   respiratory-related causes and other respiratory morbidity endpoints has increased markedly since

4   the 1996 PM AQCD. In addition to evaluating statistical relationships for PM_{10}, quite a few new

5   studies also evaluated other PM metrics. Those providing estimates of increased risk in U.S. and

6   Canadian cities for respiratory-related morbidity measures (hospitalizations, respiratory

7   symptoms, etc.) in relation to 24-h increments in ambient fine particles ($PM_{2.5}$) or coarse fraction

8   ($PM_{10-2.5}$) of inhalable thoracic particles are included in Tables 9-12 and 9-13, respectively.

9

10   **Respiratory-Related Hospital Admission/Visits.** PM hospital admissions/ visit studies that

11   evaluated excess risks in relation to PM_{10} measures are still quite informative. Maximum excess

12   risk estimates for PM_{10} associations with respiratory-related hospital admissions and visits in

13   U.S. cities are shown in Figure 9-28. Nearly all the studies showed positive, statistically

14   significant relationships between ambient PM_{10} and increased risk for respiratory-related doctors'

15   visits and hospital admissions. Overall, the results substantiate well ambient PM_{10} impacts on

16   respiratory-related hospital admissions/visits. The excess risk estimates fall most consistently in

17   the range of 5 to 25.0% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma hospital admissions

18   and doctor's visits being higher than for COPD and pneumonia hospitalization. Other, more

19   limited, new evidence (not depicted in Figure 9-10) shows excess risk estimates for overall

20   respiratory-related or COPD hospital admissions falling in the range of 5 to 15.0% per 24-h

21   25 $\mu g/m^3$ increment in $PM_{2.5}$ or $PM_{10-2.5}$. Larger estimates are found for asthma admissions or

22   physician visits, ranging up to ca. 40 to 50% for children <18 yr old in one study.

23   Of particular note in Figure 9-28 are the large effect size estimates now being reported for

24   asthma hospitalizations and visits. Very importantly, these hospital admission/visit studies and

25   other new studies on respiratory symptoms and lung function decrements in asthmatics are

26   emerging as possibly indicative of ambient PM likely being a notable contributor to exacerbation

27   of asthma. Additional evidence for PM-asthma effects is also emerging from panel studies of

28   lung function and respiratory symptoms, as discussed below.

29   New panel studies of lung function and respiratory symptoms in asthmatic subjects have

30   been conducted by more than 10 research teams in various locations world-wide. As a group, the

31   studies examine health outcome effects that are similar, such as pulmonary peak flow rate
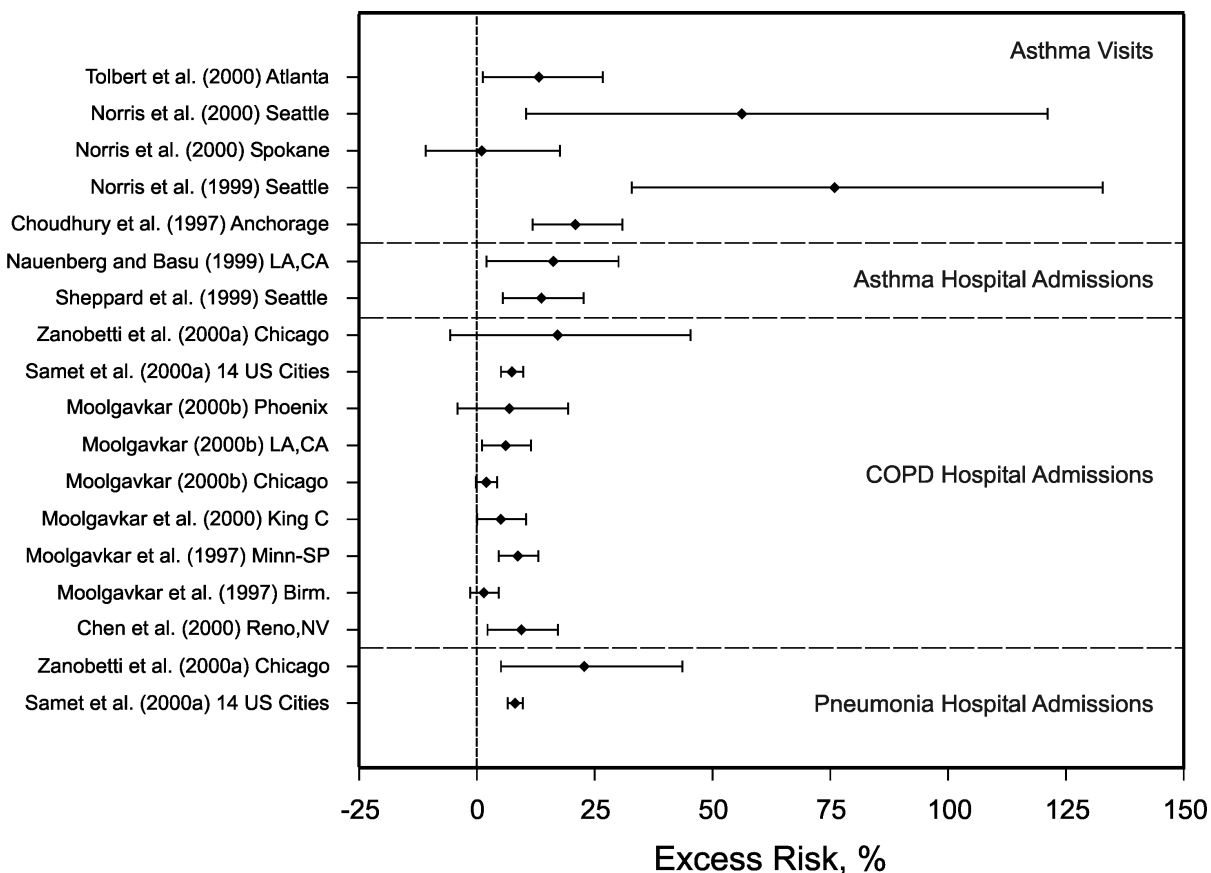
Figure 9-28. **Maximum excess risk in selected studies of U.S. cities relating PM_{10} estimate of exposure (50 μg/m³) to respiratory-related hospital admissions and visits.**

1   (PEFR); and the studies typically characterize the clinical-symptomatic aspects in a sample of

2   mild to moderate asthmatics (mainly children aged 5 to 16 yrs) observed in their natural setting.

3   Their asthma typically is being treated to keep them symptom free (with "normal" pulmonary

4   function rates, and activity levels) and to prevent recurrent exacerbations of asthma. Severity of

5   their asthma is characterized by symptom, pulmonary function, and medication use and would be

6   classified to include mild intermittent to mild persistent asthma suffers (National Institutes of

7   Health, 1997). As a group, they may thusly differ from asthmatics examined in studies of

8   hospitalization or doctor visits for acute asthmatic episodes, who may have more severe asthma.

9   Most studies reported ambient PM_{10} results, but $PM_{2.5}$ was examined in two studies. Other

10   ambient PM measures (BS and SO_4) also were used. For these studies, mean PM_{10} levels range

1   from a low of 13 μg/m^3 in Finland to a high of 167 μg/m^3 in Mexico City. The Mexico City

2   level is over three times more than each of the other levels and is unique compared to the others.

3   Related 95% CI for these means or ranges show 1-day maximums above 100 μg/m^3 in four

4   studies, with two of these above 150 μg/m^3. Hence, these studies mainly evaluated different PM

5   metrics indexing PM concentrations in the range found in U.S. cities (see Chapter 3). All the

6   studies controlled for temperature, and several controlled for relative humidity.

7   Many panel studies are analyzed using a design that takes advantage of the repeated

8   measures on the same subject. Study subject number (N) varied from 12 to 164, with most

9   having N >50; and all gathered adequate subject-day data to provide sufficient power for their

10   analyses. Linear models often are used for lung function and logistic models for dichotomous

11   outcomes. Meteorological variables are used as covariates; and medication use is also sometimes

12   evaluated as a dependent variable or treated as an important potential confounder. However,

13   perhaps the most critical choice in the model is selection of the lag for the pollution variable.

14   Presenting lag periods with only the strongest associations introduces potential bias, because the

15   biological basis for lag structure may be related to effect. No biological bases for pertinent lag

16   periods are known, but some hypotheses can be proposed. Acute asthmatic reactions can occur

17   4 to 6 h after exposure and, thus, 0-day lag may be more appropriate than 1-day lags for that

18   acute reaction. Lag 1 may be more relevant for morning measurement of asthma outcome from

19   PM exposure the day before, and longer term lags (i.e., 2 to 5 days) may represent the outcome of

20   a more prolonged inflammatory mechanism; but too little information is now available to

21   predetermine appropriate lag(s).

22   Chapter 8 noted that people with asthma tend to have greater TB deposition than do healthy

23   people, but this data was not derived from the younger age group studied in most asthma panel

24   studies. The Peters et al. (1997b) study is unique for two reasons: (1) they studied the size

25   distribution of the particles in the range 0.01 to 2.5 μm and (2) examined the number of particles.

26   They reported that asthma-related health effects of 5-day means of the number of ultrafine

27   particles were larger than those of the mass of the fine particles. In contrast, Pekkanen et al.

28   (1997) also examined a range of PM sizes, but PM$_{10}$ was more consistently associated with PEF.

29   Delfino et al. (1998) is unique in that they report larger effects for 1- and 8-h maximum PM$_{10}$

30   than for the 24-h mean.

1   The results for the asthma panels of the peak flow analysis consistently show small

2   decrements for both PM_{10} and $PM_{2.5}$. The effects using 2- to 5-day lags averaged about the same

3   as did the 0 to 1 day lags. Stronger relationships often were found with ozone. The analyses

4   were not able to clearly separate co-pollutant effects. The effects on respiratory symptoms in

5   asthmatics also tended to be positive. Most studies showed increases in cough, phlegm,

6   difficulty breathing, and bronchodilator use. The only endpoint more strongly related to longer

7   lag times was bronchodilator use, which was observed in three studies. The peak flow

8   decrements and respiratory symptoms are indicators for asthma episodes.

9   For PM_{10}, nearly all of the point estimates showed decreases, but most were not statistically

10   significant, as shown in Figure 9-29 as an example of PEF outcomes. Lag 1 may be more

11   relevant for morning measurement of asthma outcome from the previous day. The figure

12   presents studies that provided this data. The results were consistent for both AM and PM peak

13   flow analyses. Similar results were found for the $PM_{2.5}$ studies, although there were fewer

14   studies. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow.

15   Of these, Gold et al. (1999), Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al. (1997),

16   and Romieu et al. (1996) all found similar results for $PM_{2.5}$ and PM_{10}. The study of Peters et al.

17   (1997b) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas (2000) found

18   larger effects for $PM_{2.5}$ than for $PM_{10-2.5}$. Naeher et al. (1999) found that H^+ was related

19   significantly to a decrease in morning PEF. Thus, there is no evidence here for a stronger effect

20   of $PM_{2.5}$ when compared to PM_{10}. Also, of studies that provided analyses that attempted to

21   separate out effects of PM_{10} and $PM_{2.5}$ from other pollutants, Gold et al. (1999) studied possible

22   interactive effects of $PM_{2.5}$ and ozone on PEF; they found independent effects of the two

23   pollutants, but the joint effect was slightly less than the sum of the independent effects.

24   The effects on respiratory symptoms in asthmatics also tended to be positive, although

25   much less consistent than the lung function effects. Most studies showed increases in cough,

26   phlegm, difficulty breathing, and bronchodilator use (although generally not statistically

27   significant), as shown in Figure 9-30 for cough as an example. Three studies included both PM_{10}

28   and $PM_{2.5}$ in their analyses. The studies of Peters et al. (1997c) and Tiittanen et al. (1999) found

29   comparable effects for the two measures. Only the Romieu et al. (1996) found slightly larger

30   effects for $PM_{2.5}$. These studies also give no good evidence for a stronger effect of $PM_{2.5}$ when

31   compared to PM_{10}.
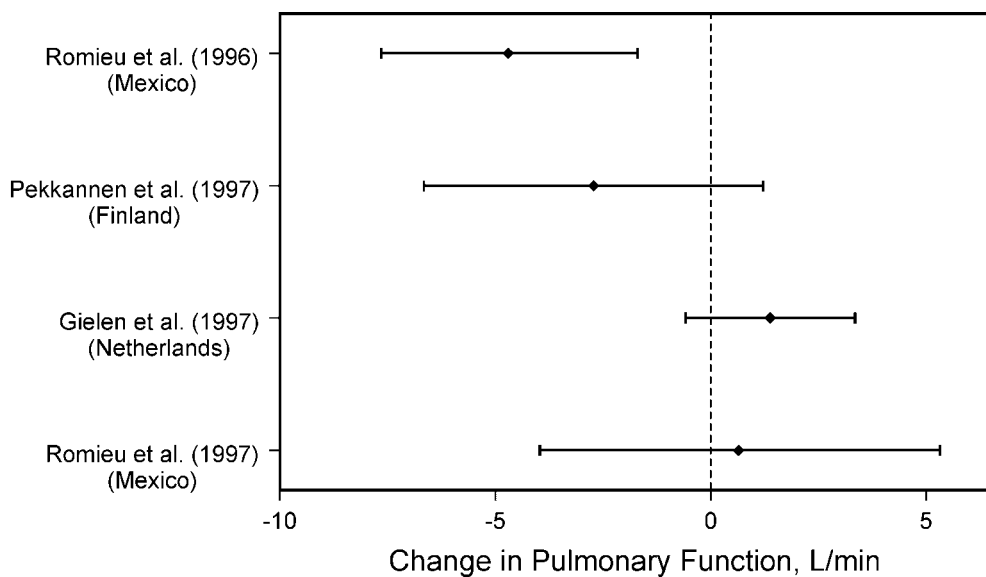
Figure 9-29. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 μg/m³ PM$_{10}$ on morning peak flow lagged 1 day.
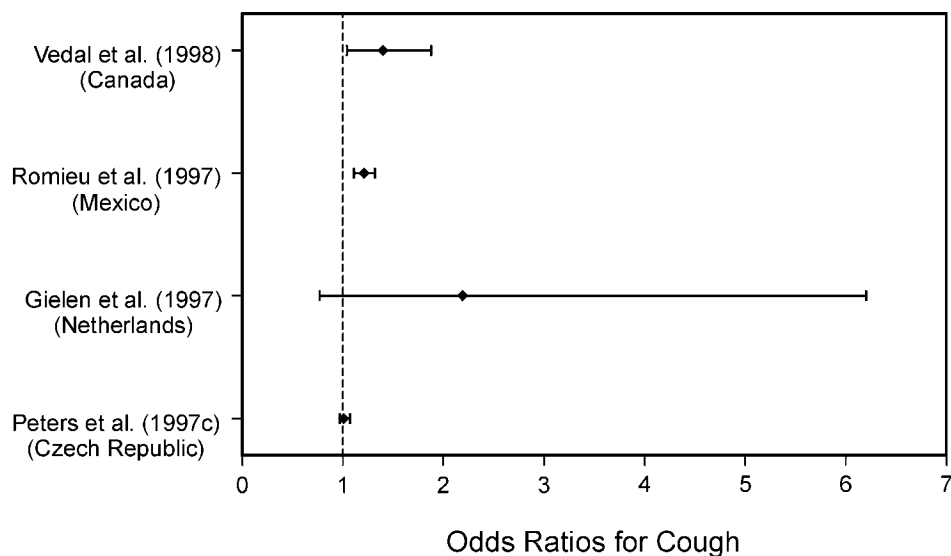
Figure 9-30. Odds ratios for cough for a 50-μg/m³ increase in PM$_{10}$ for selected asthmatic children studies, with lag 0 with 95% CI.

1   The results of PM_{10} peak flow analyses for nonasthmatic populations were inconsistent.

2   Fewer studies reported results in the same manner as the asthmatic studies. Many of the point

3   estimates showed increases rather than decreases. $PM_{2.5}$ studies found similar results. The

4   effects on respiratory symptoms in nonasthmatics were similar to those in asthmatics: most

5   studies showed that PM_{10} increases cough, phlegm, and difficulty breathing, but these increases

6   were generally not statistically significant. Schwartz and Neas (2000) found that $PM_{10-2.5}$ was

7   significantly related to cough. Tiittanen et al. (1999) found that 1-day lag of $PM_{10-2.5}$ was related

8   to morning PEF, but not evening PEF. Neas et al. (1999) found no association of $PM_{10-2.5}$ with

9   PEF in non-asthmatic subjects.

10

11   ***Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory***
12   ***Symptoms***

13   In the 1996 PM AQCD, the available respiratory disease studies were limited in terms of

14   conclusions that could be drawn. At that time, three studies based on a similar type of

15   questionnaire administered at three different times as part of the Harvard Six-City and 24-City

16   Studies provided data on the relationship of chronic respiratory disease to PM. All three studies

17   suggest a chronic PM exposure effect on respiratory disease. The analysis of chronic cough,

18   chest illness, and bronchitis tended to be significantly positive for the earlier surveys described

19   by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one,

20   Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and

21   Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with highest

22   exposure of strongly acidic particles when compared with the least polluted community. Fine

23   PM sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12,

24   2.42).

25   The studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) all had

26   good monitoring data and well-conducted standardized pulmonary function testing over many

27   years, but showed no effect on children of PM pollution indexed by TSP, PM_{15}, $PM_{2.5}$, or

28   sulfates. In contrast, the later 24-city analyses reported by Raizenne et al. (1996) found

29   significant associations of effects on FEV_1 or FVC in U.S. and Canadian children with both

30   acidic particles and other PM indicators. Overall, the available studies provided limited evidence

1 suggestive of pulmonary lung function decrements being associated with chronic exposure to PM

2 indexed by various measures (TSP, PM_{10}, sulfates, etc.).

3   A number of studies have been published since 1996 which evaluate the effects of

4 long-term PM exposure on lung function and respiratory symptoms, as presented in Chapter 8.

5 The methodology in the long-term studies varies much more than the methodology in the short-

6 term studies. Some studies reported highly significant results (related to PM), whereas others

7 reported no significant results. Of particular note are several studies reporting associations

8 between long-term PM exposures (indexed by various measures) or changes in such exposures

9 over time and chronic bronchitis rates, consistent with the findings on bronchitis from the

10 Dockery et al. (1996) study noted above.

11   Unfortunately, the cross-sectional studies often are potentially confounded, in part, by

12 unexplained differences in geographic regions; and it is difficult to separate out results consistent

13 with a PM gradient from any other pollutants or factors having the same gradient. The studies

14 that looked for a time trend also are confounded by other conditions that changed over time. The

15 most credible cross-sectional study remains that described by Dockery et al. (1996) and Raizenne

16 et al. (1996). Whereas most studies include two to six communities, this study included 24

17 communities and is considered to provide the most credible estimates of long-term PM exposure

18 effects on lung function and respiratory symptoms.

19

20 **9.12.2.3 Methodological Issues**

21   Chapter 8 discussed several still important methodological issues related to assessment of

22 the overall PM epidemiologic database. These include, especially, issues related to model

23 specifications and consequent adequacy of control for potentially confounding of PM effects by

24 co-pollutants, evaluations of possible source relationships to pollutant effects that may be useful

25 in sorting out better effects attributable to PM versus other co-pollutants or both, and other issues

26 such as lag structure. Key points are discussed concisely below.

27

28 *Time Series Studies: Confounding by Co-Pollutants in Individual Cities*

29   The co-pollutant issue was discussed at length in the 1996 document and still remains an

30 important issue. It must be recognized that there are large differences in concentrations of

31 measured gaseous co-pollutants (and presumably unmeasured pollutants as well) in different

1   parts of the United States, as well as the rest of the world; and the concentrations are often

2   correlated with concentrations of PM and its components because of commonality in source

3   emissions, wind speed and direction, atmospheric processes, and other human activities and

4   meteorological conditions. Large sources in the United States include motor vehicle emissions

5   (gasoline combustion, diesel fuel combustion, evaporation, particles generated by tire wear, etc.),

6   coal combustion, fuel oil combustion, industrial processes, residential wood burning, solid waste

7   combustion, and so on. Thus, one might reasonably expect some large correlations among PM

8   and co-pollutants, but possibly with substantial differences in relation by season in different

9   cities or regions. Statistical theory suggests that PM and co-pollutant effect size estimates will be

10   highly unstable and often insignificant in multi-pollutant models when collinearity exists. Many

11   recent studies demonstrate this effect, for both hospital admissions (Moolgavkar, 2000b) and

12   mortality (Moolgavkar, 2000a; Chock et al., 2000). Because the problem seems largely insoluble

13   in studies in single cities, the new multi-city studies (Samet et al., 2000a,b; Schwartz, 1999;

14   Schwartz and Zanobetti, 2000) have provided important new insights. See discussions of

15   NMMAPS analysis in Chapter 8 and below for discussion of issues related to control for

16   co-pollutant effects. Overall, although such issues may warrant further evaluation, it now

17   appears unlikely that such confounding accounts for the vast array of effects attributed to ambient

18   PM based on the rapidly expanding PM epidemiology database.

19   Numerous new studies have reported associations not only between PM, but also gaseous

20   pollutants (O_3, SO_2, NO_2, and CO), and mortality. In many of these studies, simultaneous

21   inclusion of one or more gaseous pollutants in regression models did not markedly affect PM

22   effect size estimates, as was generally the case in the NMMAPS analyses for 90 cities (see

23   Figure 9-31). On the other hand, some studies reporting positive and statistically significant

24   effects for gaseous copollutants (e.g., O_3, NO_2, SO_2, CO) found varying degrees of robustness of

25   their effects estimates or those of PM in multi-pollutant models as discussed in Chapter 8

26   (Section 8.4). Thus, it is likely that there are independent health effects of PM and gaseous

27   pollutants, there is not yet sufficient evidence by which to confidently separate out fully the

28   relative contributions of PM versus those of other gaseous pollutants or by which to quantitate

29   modifications of PM effects by other co-pollutants, including possible synergistic interactions

30   that may vary seasonally or from location to location. Overall, it appears, however, that ambient

31   PM and O_3 can be most clearly separated out as likely having independent effects, their
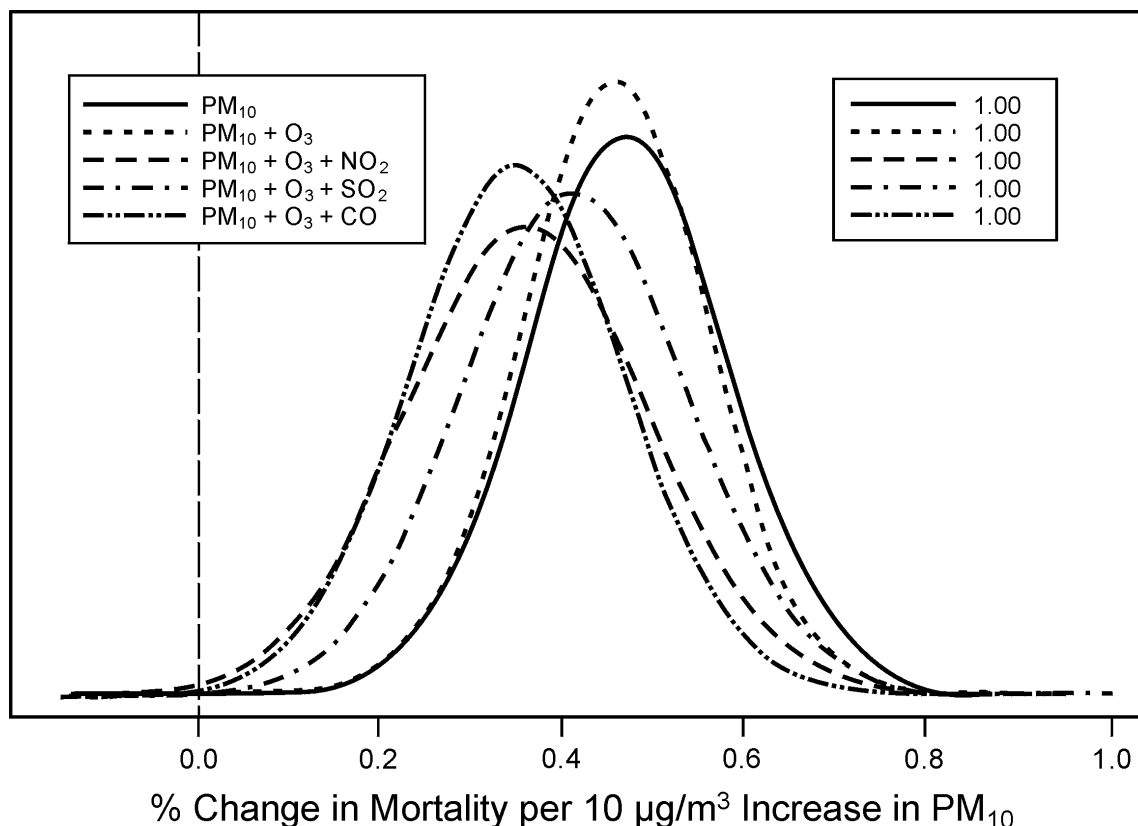
Figure 9-31. Marginal posterior distributions for effect of PM$_{10}$ on total mortality at lag 1, with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Samet et al. (2000a,b).

1   concentrations often not being highly correlated. More difficulty is encountered, at times, in

2   sorting out whether NO$_2$, CO, or SO$_2$ are exerting independent effects in cities where they tend to

3   be highly correlated with ambient PM concentrations, possibly because of derivation of

4   important PM constituents from the same source (e.g., NO$_2$, CO, PM from mobile sources) or a

5   gaseous pollutant (e.g., SO$_2$) serving as a precursor for a significant PM component (e.g.,

6   sulfate). However, other information discussed in Section 8.4 on conceptual frameworks for

7   evaluating possible confounding makes it clear that diagnostic evaluations of inflation or

8   deflation of PM effect size estimates by addition of gaseous co-pollutants into multiple pollutant

1	models, at best, may indicate potential confounding of PM effects in a given analysis. Other
2	independently-derived exposure analyses, i.e., Sarnat et al. (2000, 2001), however, strongly
3	suggest a very low probability of observed PM effects being due to confounding with gaseous
4	criteria pollutants (CO, NO_2, SO_2, O_3).
5	
6	***Time Series Studies: Model Selection for Lags, Moving Averages, and Distributed Lags***
7	A number of different approaches have been used to evaluate the temporal dependence of
8	mortality or morbidity on time-lagged PM concentrations, including unweighted moving
9	averages of PM concentrations over one or more days, general weighted moving averages, and
10	polynomial distributed moving averages. Unless there are nearly complete daily data, each
11	different lag will be using a different set of mortality data corresponding to spaced PM
12	measurement; for example, for lag 0 with every-sixth-day PM measurements, the mortality data
13	are on the same day as the PM data, for lag 1 the mortality data are on the next day after the PM
14	data, and so on. Although this effect is likely to be small, it should nonetheless be kept in mind.
15	The issue of dealing with lag structure, which may not necessarily be the same for all cities
16	or for all regions, can be illustrated by NMMAPS findings. As shown in Table 9-19, the rank
17	ordering of effects by lag days differs somewhat among NMMAPS regions. The combined data
18	set suggests that lag 1 provides the best fit, but with some regional differences. This raises the
19	question as to whether a single lag model should be assumed to characterize a diverse set of
20	regional findings. Because the particle constituents, co-pollutants, susceptible subpopulations,
21	and meteorological covariates are likely to differ substantially from one region to another, the
22	timing of the largest mortality effects also may be presumed to differ in at least some cases. This
23	undoubtedly contributes to the variance of the estimated effects.
24	The distributed lag models used in the NMMAPS II morbidity studies are a noteworthy
25	methodological advance. The fitted distributed lag models showed significant heterogeneity
26	across cities for COPD and pneumonia, however (see Table 15 therein), again raising the
27	question of how heterogeneous effects can best be combined so as not to obscure potentially real
28	city-specific or region-specific differences.
29	Only three cities with nearly complete daily PM_{10} data were used to evaluate more general
30	multi-day lag models (Chicago, Minneapolis/St. Paul, Pittsburgh), and these show somewhat
31	different patterns of effect, with lag 0 < lag 1 and lag 1 >> lag 2 for Chicago, lag 0 = lag 1 > lag 2

**TABLE 9-19. PERCENT INCREASE IN MORTALITY PER 10 μg/m^3 PM$_{10}$
IN SEVEN U.S. REGIONS (from Figure 23 in NMMAPS II)**

Region	Rank Order of Effects by Lags
Northwest	lag 0 < lag 1 = lag 2
Southwest	lag 0 < lag 1 < lag 2
Southern California	lag 0 < lag 1, lag 1 > lag 2, lag 0 < lag 2
Upper Midwest	lag 0 > lag 1, lag 0 > lag 2, lag 1 < lag 2
Industrial Midwest	lag 0 < lag 1, lag 1 > lag 2
Northeast	lag 0 < lag 1, lag 1 >> lag 2
Southeast	lag 0 << lag 1, lag 1 > lag 2
Combined	lag 0 < lag 1, lag 1 > lag 2

1   for Minneapolis, and lag 0 < lag 1 = lag 2 for Pittsburgh. The 7-day distributed lag model is

2   significant for Pittsburgh, but less so in the other cities. The remaining data are limited

3   intrinsically in what they can reveal about temporal structure.

4

5   ***Time Series Studies: Model Selection for Concentration-Response Functions***

6   Given the number of analyses that needed to be performed, it is not surprising that most of

7   the NMMAPS studies focused on linear concentration-response models. More recent studies

8   (Daniels et al., 2000) for the 20 largest U.S. cities have found posterior mean effects of 2 to 2.7%

9   excess risk of total daily mortality per 50 μg/m^3 24-h PM$_{10}$ at lags 0, 1, 0+1 days; 2.4 to 3.5%

10   excess risk of cardiovascular and respiratory mortality; and 1.2 to 1.7% for other causes of

11   mortality. The posterior 95% credible regions are all significantly greater than 0. However, the

12   threshold models gave distinctly different estimates of 95% credible regions for the threshold for

13   total mortality (15 μg/m^3 at lag 1, range 10 to 20), cardiovascular and respiratory mortality

14   (15 μg/m^3 at lag 0+1, range 0 to 20), and other causes of mortality (65 μg/m^3 at lag 0+1, range

15   50 to 75 μg/m^3).

16   Another problem is that the shape of the relationship between mortality and PM$_{10}$ may

17   depend, to some extent, on the associations of PM$_{10}$ with gaseous co-pollutants. The association

1   is not necessarily linear, and is indeed likely to have both seasonal and secular components that

2   depend on the city location. Thus, further elaborations of these models may be desirable.

3

4   *Effects of Exposure Error in Daily Time Series Epidemiology*

5   There has been considerable controversy over how to deal with the nonambient component

6   of personal exposure. Recent biostatistical analyses of exposure error have indicated that the

7   nonambient component will not bias the statistically calculated risk in community time-series

8   epidemiology, provided that the nonambient component of personal exposure is independent of

9   the ambient concentration. Consideration of the random nature of nonambient sources and recent

10   studies, in which estimates of α, ambient-generated PM divided by ambient PM concentrations,

11   have been used to estimate separately the ambient-generated and nonambient components of

12   personal exposure, support the assumption that the nonambient exposure is independent of the

13   ambient concentration. Therefore, it is reasonable to conclude that community time series

14   epidemiology describes statistical associations between health effects and exposure to ambient-

15   generated PM, but does not provide any information on possible health effects resulting from

16   exposure to nonambient PM (e.g., indoor-generated PM).

17   From the point of view of exposure error, it is also significant to note that, although

18   ambient concentrations of a number of gaseous pollutants (O_3, NO_2, SO_2) often are found to be

19   highly correlated with various PM parameters, personal exposures to these gases are not

20   correlated highly with personal exposure to PM indicators. The correlations of the ambient

21   concentrations of these gases also are not correlated highly with the personal exposure to these

22   gases. Therefore, when significant statistical associations are found between these gases and

23   health effects, it could be that these gases may, at times, be serving as surrogates for PM rather

24   than being causal themselves. Pertinent information on CO has not been reported.

25   The attenuation factor, α, is a useful variable. For relatively constant α, the risk because of

26   a personal exposure to 10 $\mu g/m^3$ of ambient PM is equal 1/α times the risk from a concentration

27   of 10 $\mu g/m^3$ of ambient PM, where α varies from a low of 0.1 to 0.2 to a maximum of 1.0. (The

28   health risk for an interquartile change in ambient concentration of PM is the same as that for an

29   interquartile change in exposure to ambient PM). Differences in α among cities, reflecting

30   differences in air-exchange rates (e.g., because of variation in seasonal temperatures and in extent

31   of use of air conditioners) and differences in indoor/outdoor time ratios, may, in part, account for

1   any differences in risk estimates based on statical associations between ambient concentrations

2   and health effects for different cities or regions. If α were 0.3 in city A, but 0.6 in city B, and the

3   risks for an increase in personal exposure of 10 μg/m^3 were identical, then a regression of health

4   effects on ambient concentrations would yield a health risk for city B that would be twice that

5   obtained for city A.

6   A number of exposure analysts have discussed the PM exposure paradox (i.e., that

7   epidemiology yields statistically significant associations between ambient concentrations and

8   health effects even though there is a near zero correlation between ambient concentrations and

9   personal exposure in many studies). Several explanations have been advanced to resolve this

10   paradox. First, personal exposure contains both an ambient-generated and a nonambient

11   component. Community time series epidemiology yields information only on the ambient-

12   generated component of exposure. Therefore, the appropriate correlation to investigate is the

13   correlation between ambient concentration and personal exposure to ambient-generated PM, not

14   between ambient concentrations and total personal exposure (i.e., the sum of ambient-generated

15   and nonambient PM). Second, biostatistical analysis of exposure error indicates that if the risk

16   function is linear in the PM indicator, the average of the sum of the individual risks (risk function

17   times individual exposure) may be replaced by the risk function times the community average

18   exposure. Thus, the appropriate correlation (of ambient concentrations and ambient-generated

19   exposure) is not the pooled correlation of different days and different people but the correlation

20   between the daily ambient concentrations and the community average daily personal exposure to

21   ambient-generated PM. Because the nonambient component is not a function of the ambient

22   concentration, its average will tend to be similar each day. Therefore, the correlation coefficient

23   will depend on α but not on the nonambient exposure. These types of correlation yield high

24   correlation coefficients.

25   A few studies have conducted simulation analyses of effects of measurement errors on the

26   estimated PM mortality effects. These studies suggest that ambient PM excess risk effects are

27   more likely underestimated than overestimated, and that spurious PM effects (i.e., qualitative

28   bias such as change in the sign of the coefficient) because of transferring of effects from other

29   covariates require extreme conditions and are therefore very unlikely. The error because the

30   difference between the average personal exposure and the ambient concentration is likely the

1   major source of bias in the estimated relative risk. One study also suggested that apparent linear

2   exposure-response curves are unlikely to be artifacts of measurement error.

3   In conclusion, for time-series epidemiology, ambient concentration is a useful surrogate for

4   personal exposure to ambient-generated PM, although the risk per unit ambient PM

5   concentration is biased low by the factor α compared to the risk per unit exposure to ambient-

6   generated PM. Epidemiologic studies of statistical associations between long-term effects and

7   long term ambient concentrations compare health outcome rates across cities with different

8   ambient concentrations. Ordinarily, PM exposure measurement errors are not expected to

9   influence the interpretation of findings from either the community time-series or long-term

10   epidemiologic studies that have used ambient concentration data if they include sufficient

11   adjustments for seasonality and key personal and geographic confounders. When individual level

12   health outcomes are measured in small cohorts, to reduce exposure misclassification errors, it is

13   essential that better real-time exposure monitoring techniques be used and that further speciation

14   of indoor-generated, ambient, and personal PM mass be accomplished. This should enable

15   measurement (or estimation) of both ambient and nonambient components of personal exposure

16   and evaluation of the extent to which personal exposure to ambient-generated PM, personal

17   exposure to nonambient PM, or total personal exposure (to ambient-generated plus nonambient

18   PM) contribute to observed health effects.

19

20   ### 9.12.3 Coherence of Reported Epidemiologic Findings

21   **Interrelationships Between Health Endpoints.** Considerable coherence exists across

22   newly available epidemiologic study findings. For example, it was earlier noted that effects

23   estimates for total (nonaccidental) mortality generally fall in the range of 2.5 to 5.0% excess

24   deaths per 50 μg/m^3 24-h PM$_{10}$ increment. These estimates comport well with those found for

25   cause-specific cardiovascular- and respiratory-related mortality. Furthermore, larger effect sizes

26   for cardiovascular (in the range of 3 to 6% per 50 μg/m^3 24-h PM$_{10}$ increment) and respiratory (in

27   the range of 5 to 25% per 50 μg/m^3 24-h PM$_{10}$) hospital admissions and visits are found, as

28   would be expected versus those for PM$_{10}$-related mortality. Also, several independent panel

29   studies, evaluating temporal associations between PM exposures and measures of heart beat

30   rhythm in elderly subjects, provide generally consistent indications of decreased heart rate (HR)

31   variability being associated with ambient PM exposure (decreased HR variability being an

1   indicator of increased risk for serious cardiovascular outcomes, e.g., heart attacks). Other studies

2   point toward changes in blood characteristics (e.g., increased C-reactive protein levels) related to

3   increased risk of ischemic heart disease as also being associated with ambient PM exposures.

4

5   **Spatial Interrelationships.** Both the NMMAPS and Cohort Reanalyses studies had a

6   sufficiently large number of cities to allow considerable resolution of regional PM effects within

7   the "lower 48" states, but this approach was taken much farther in the Cohort Reanalysis studies

8   than in NMMAPS. There were 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities

9   with $PM_{2.5}$ and 151 cities with sulfates in Pope et al. (1995) and in the reanalyses using the

10   original data; and, in the additional analyses by the cohort study reanalysis team, 63 cities with

11   $PM_{2.5}$ data and 144 cities with sulfate data. The relatively large number of data points allowed

12   estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with

13   resolution on a scale of a few tens to hundreds of kilometers. Information drawn from the maps

14   presented in Figures 16-21 in Krewski et al. (2000) is summarized below.

15   The patterns are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface

16   (Krewski, Figure 18) has peak levels in the industrial midwest, including the Chicago and

17   Cleveland areas, the upper Ohio River Valley, and around Birmingham, AL. Lower, but

18   elevated, $PM_{2.5}$ is found almost everywhere else east of the Mississippi, as well as in southern

19   California. This is rather similar to the modeled sulfate surface (Krewski, Figure 16), with the

20   absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only region with

21   elevated SO_2 concentrations is the Cleveland-Pittsburgh area. A preliminary evaluation is that

22   secondary sulfates in particles derived from local SO_2 is more likely to be important in the

23   industrial midwest, south from the Chicago-Gary region and along the upper Ohio River region.

24   This intriguing pattern may be related to the combustion of high-sulfur fuels in the subject areas.

25   The overlay of mortality and air pollution is also of interest. The spatial overlay of long-

26   term $PM_{2.5}$ and mortality (Krewksi, Figure 21) is highest for the upper Ohio River region, but

27   also includes a significant association over most of the industrial midwest from Illinois to the

28   eastern noncoastal parts of North Carolina, Virginia, Pennsylvania, and New York. This is

29   reflected, in diminished form, by the sulfates map (Krewski, Figure 19) where the peak sulfate-

30   mortality associations occur somewhat east of the peak $PM_{2.5}$-mortality associations. The SO_2

31   map (Krewski, Figure 20) shows peak associations similar to, but slightly east of, the peak

1   sulfate associations. This suggests that, although SO_2 may be an important precursor of sulfates

2   in this region, there may be other considerations (e.g., metals) in the association between $PM_{2.5}$

3   and long-term mortality, embracing a wide area of the midwest and northeast (especially

4   noncoastal areas).

5   It should be noticed that, although a variety of spatial modeling approaches were discussed

6   in the NMMAPS methodology report (NMMAPS Part I, pp. 66-71), the primary spatial analyses

7   in the 90-city study (NMMAPS, Part II) were based on a simpler seven-region breakdown of the

8   contiguous 48 states. The 20-city results reported for the spatial model in NMMAPS I show a

9   much smaller posterior probability of a PM_{10} excess risk of short-term mortality, with a spatial

10 posterior probability versus a nonspatial probability of a PM_{10} effect of 0.89 versus 0.98 at lag 0,

11 of 0.92 versus 0.99 at lag 1, and of 0.85 versus 0.97 at lag 2. The evidence that PM_{10} is

12 associated with an excess short-term mortality risk is still moderately strong with a spatial model,

13 but much less strong than with a nonspatial model. In view of the sensitivity of the strength of

14 evidence to the spatial model, the model assumptions warrant additional study. Even so, there is

15 a considerable degree of coherence between the long-term and short-term mortality findings of

16 the studies, with stronger evidence of a modest but significant short-term PM_{10} effect and a larger

17 long-term fine particle ($PM_{2.5}$ or sulfate) effect in the industrial midwest. The short-term effects

18 are larger but less certain in southern California and the northeast, whereas the long-term effects

19 seem less certain there.

20

21

22 **9.13 EVALUATION OF STATISTICAL AND MEASUREMENT**
23 **ERROR ISSUES**

24 **9.13.1 Errors Related to Concentration, Exposure, and Dose**

25 *What Is the Effect of Measurement Error and Misclassification on Estimates of the*
26 *Association Between Air Pollution and Health?*

27   In PM epidemiology, statistical models are developed that relate heath effects to some

28 measurement of ambient PM. However, if PM is toxic, the most direct relationship should be

29 between health effects and PM dose. Therefore, in PM epidemiology, ambient PM

30 concentrations must be considered a surrogate for PM dose. In going from ambient PM

31 concentrations to PM dose, there are many possibilities for introducing error or variability. This

1 section will discuss such possibilities and, to the extent information is available, the influence of

2 such errors on the variability in epidemiologic results.
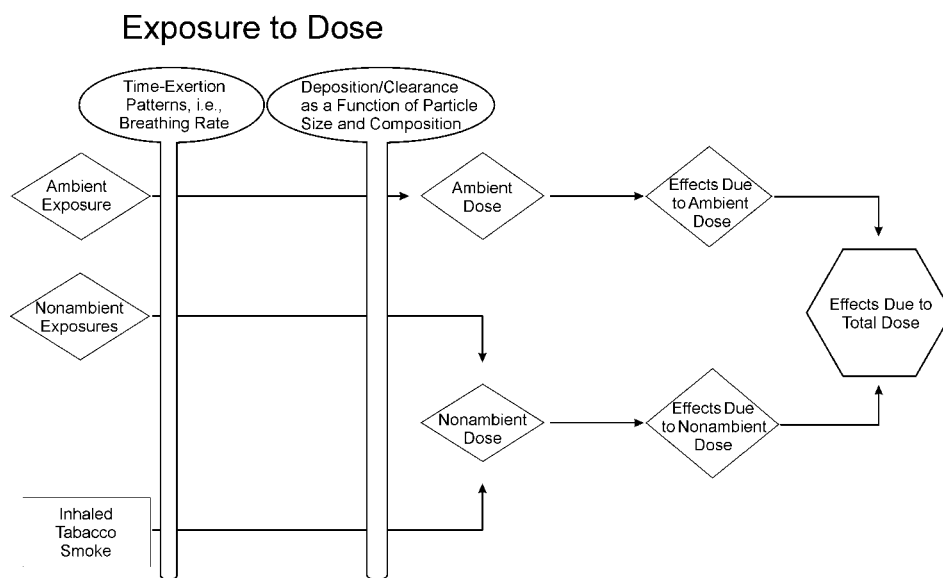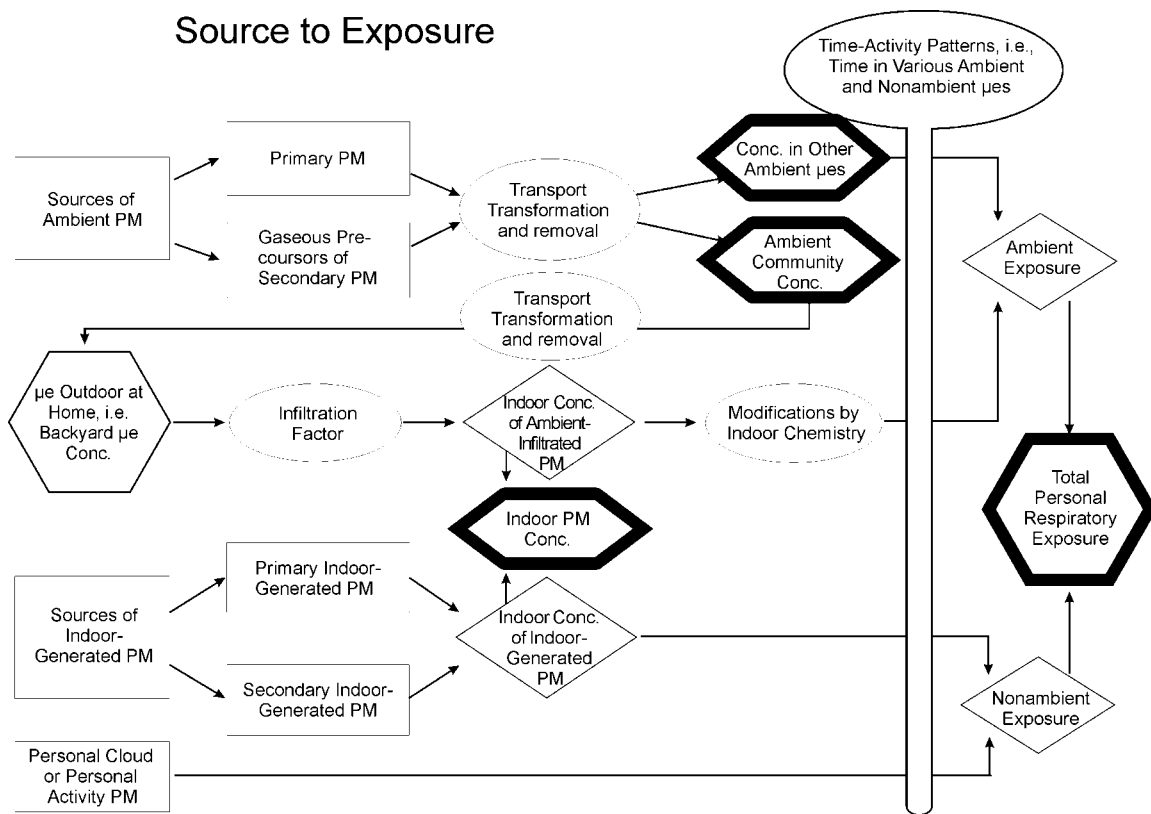
3   Figure 9-32 shows an expanded version of the Risk Assessment Framework giving in more

4 detail the various processes involved in going from PM sources to PM dose. In Figure 9-32,

5 variables that can be measured directly are enclosed in hexagons; variables that cannot be

6 measured directly but can be estimated are enclosed in diamonds; and processes that influence

7 the relationship between ambient PM concentrations and PM dose are enclosed in ovals. There

8 are many opportunities for error in going from ambient concentrations to dose.

9

10 **9.13.1.1 Opportunities for Error in the Use of Ambient PM Concentration as a**
11 **Surrogate for PM Dose in Epidemiologic Studies**

12 *Measurement of PM Concentrations*

13   As discussed in Chapter 2, Section 2.2.2.6, since there is no standard reference material that

14 can represent suspended PM, there cannot be any real determination of the accuracy with which

15 the concentration of suspended PM is measured. The precision of the measurement can be

16 determined by comparison of results from several collocated monitors. The mass of PM,

17 collected on a filter and equilibrated for 24 hours at 25 C and 40% relative humidity according to

18 the Federal Reference Method, can be measured with high precision. The precision of a

19 measurement of $PM_{10-2.5}$ is normally less than that of $PM_{2.5}$ but can be nearly as high if special

20 care is taken. The measurement of ultrafine PM ($PM_{0.1}$) presents special problems and little is

21 known about the accuracy or precision of such measurements.

22   As discussed in Chapter 2, Section 2.2.2.1, a major problem in the measurement of PM_{10}

23 and especially $PM_{2.5}$, is the variable loss of semivolatile components of PM. The most important

24 are particle-bound water (PBW), ammonium nitrate, and semivolatile organic compounds.

25 During equilibration, much of the PBW is lost and the remainder is stable at the low, constant

26 relative humidity of equilibration. However, variable fractions of the other semivolatile

27 components are also lost during sampling or equilibration (Figure 9-33). For continuous

28 monitors, the collection surface must be changed at least every hour or the PM must be dried

29 in situ. Otherwise, changes in relative humidity will cause changes in the amount of PBW which

30 will cause large changes in perceived mass. Techniques which use heating to remove PBW may

31 also remove portions of the ammonium nitrate and semivolatile organic compounds which in

Figure 9-32. An expanded version of the Risk Assessment Framework: (a) PM sources to PM exposure, (b) PM exposure to PM dose.
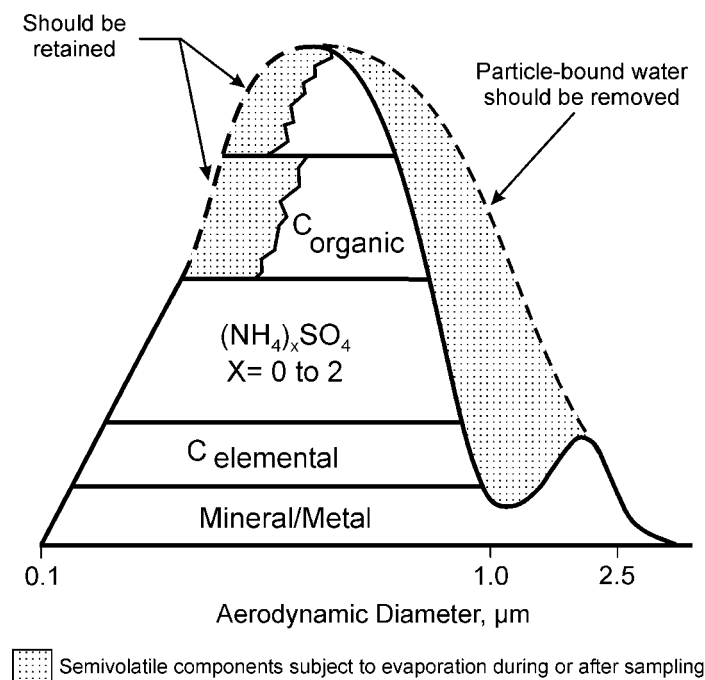
Figure 9-33. Schematic showing major nonvolatile and semivolatile components of $PM_{2.5}$. Semivolatile components are subject to partial to complete loss during equilibration or heating. The optimal technique would be to remove all particle-bound water but no ammonium nitrate or semivolatile organic PM.

1   some cases could be on the order of 50% of the total suspended PM mass. Thus, current

2   measurements of PM mass have uncertainties and variability relative to the mass of PM

3   suspended in the atmosphere. Since most of the semivolatile components are in the

4   accumulation mode, this is a more serious problem for $PM_{2.5}$ measurements than for $PM_{10-2.5}$

5   measurements. As discussed in Chapter 2, Section 2.3, several new techniques are being tested

6   which may allow removal of PBW without loss of the semivolatile components of PM.

7   However, no such measurements of PM mass have been used in epidemiologic studies. Most

8   currently available epidemiologic studies used PM indicators which measure only the relatively

9   nonvolatile components of PM. Likewise, except for the new studies using in-situ concentrated

10   ambient air particles, most toxicologic studies of ambient air particles have used filter-collected

11   material which contains only the relatively nonvolatile components of PM. Therefore, little

12   information is available on the possible health effects of the semivolatile components of PM.

1 *Errors Due to Inadequate Resolution of PM Measurements by Size, Composition, and Source*

2   Another source of error, with implications for epidemiology, is lumping together PM

3 components that behave differently with respect to processes that influence the relationship

4 between concentration and exposure, dose, and toxicity. This includes use of PM_{10}

5 measurements instead of separate measurements of $PM_{2.5}$ and $PM_{10-2.5}$, measurement of PM mass

6 rather than individual chemical components, and measurement of mass instead of contributions

7 from specific source categories. Examples of the results obtained form improved resolution are

8 shown in Tables 9-20 through 9-22. As shown in Table 9-20, only two studies found a

9 statistically significant relationship (t > 1.96) for both $PM_{2.5}$ and $PM_{10-2.5}$. In most cases, only one

10 or the other size fraction was significant. However, in each case the most significant fraction

11 showed a higher % excess risk per$\mu g/m^3$ and a greater t-statistic than was found for PM_{10}. When

12 chemical components are treated separately (Table 9-21) the statistical significance may be

13 reduced compared to $PM_{2.5}$, but the % excess risk per $\mu g/m^3$ is higher than for $PM_{2.5}$. Similarly,

14 when $PM_{2.5}$ is split into orthogonal factors, representative of different source categories (Table

15 9-22), the % excess risk increases even though the t values are slightly smaller. The inclusion of

16 some fraction of coarse mode particles in $PM_{2.5}$ may be a source of error in locations with high

17 and variable concentrations of thoracic coarse PM. A related error may occur from the use of 24-

18 hour average concentrations if the health effect is more closely related to peak dose than to

19 integrated dose.

20

21 *Frequency of PM Measurements*

22   Most epidemiologic studies have relied on monitoring data from existing networks, some

23 of which provide only every-6th-day monitoring data. This represents a loss of information

24 compared to having every day monitoring data. In addition, a level of uncertainty is introduced

25 into the estimation of the lag structure (the variation of PM effect as a function the number of

26 days between exposure and the observation of the health effect) since each lag day is based on a

27 different day of health effects. If everyday measurements of PM are available, each lag day is

28 based on health effects measured on the same day. The use of every-sixth day measurements

29 may also lead to errors in estimating annual and seasonal averages and distributions.

30

31

TABLE 9-20. PERCENT EXCESS RISK (t-statistic) PER 10 μg/m^3 INCREASE IN PM FOR THE RELATIONSHIP OF VARIOUS INDICATORS OF PM WITH VARIOUS TYPES OF MORTALITY (CV = cardiovascular) IN SEVERAL DIFFERENT LOCATIONS. IN ONLY ONE CASE WERE BOTH PM$_{2.5}$ AND PM$_{10-2.5}$ SIGNIFICANT. IN MOST CASES, THE MORE SIGNIFICANT OF THE PM$_{2.5}$ OR PM$_{10-2.5}$ SIZE FRACTION HAD A LARGER % EXCESS RISK AND T-STATISTIC THAN PM$_{10}$.

Location	Phoenix[1]	Mexico[2]	Mexico[2]	Santa Clara, Co[3]	Boston[4]	Steubenville[4]	6-Cities[4]
Mortality	CV	Total	CV	Total	Total	Total	Total
PM$_{10}$	1.9 (2.5)	1.8 (4.2)	2.0 (2.4)	1.6*	1.3 (4.9)	0.9 (2.2)	0.8 (5.8)
PM$_{2.5}$	7.1 (2.9)	1.5 (1.9)	1.6 (1.1)	3.1**	2.2 (6.3)	1.0 (1.8)	1.5 (7.4)
PM$_{10-2.5}$	2.3 (2.5)	4.1 (5.0)	4.8 (4.4)	1.5***	0.2 (0.6)	2.4 (2.4)	0.4 (1.5)

1. Mar et al., 2000. 2. Castillejos et al., 2000. 3. Fairley, 1999. 4. Swartz et al., 1996.
Significant at: *, p = 0.05; **, p = 0.01; ***, not significant.

TABLE 9-21. EXAMPLES OF HOW % EXCESS RISK PER 10 μg/m^3 INCREASE IN PM INDICATOR INCREASES FOR SPECIFIC CHEMICAL COMPONENTS OF PM. IN THIS CASE, THE T-STATISTICS TEND TO BE LOWER.

Location	Santa Clara, Co[1]	6-Cities[2]
PM$_{2.5}$	3.1	1.5
Sulfate	17.4	2.2
Nitrate	8.8	—

1. Fairley, 1999. 2. Swartz et al., 1996.

TABLE 9-22. PERCENT EXCESS RISK (t-statistic) PER INTERQUARTILE INCREASE IN PM INDICATOR FOR THE RELATIONSHIP OF VARIOUS INDICATORS OF PM WITH CARDIOVASCULAR MORTALITY FOR PHOENIX (Mar et al., 2000). FACTORS, ESTIMATED USING A FACTOR ANALYSIS SOURCE APPORTIONMENT MODEL, ARE VEHICLE EXHAUST AND RESUSPENDED ROAD DUST (vehicle), VEGETATIVE BURNING (wood), AND REGIONAL SULFATE (R. SO$_4^=$). SOURCE CATEGORIES WERE SIGNIFICANT ON DIFFERENT LAG DAYS.

	Lag Day	%ER (t)
PM$_{2.5}$	1	6.0 (2.9)
Vehicle	1	5.8 (2.6)
Wood	3	5.0 (2.7)
R. SO$_4$	0	5.7 (2.0)

Spatial Variation

2   Most epidemiologic analyses assume that the PM concentration is uniform across the

3 spatial area in which health effects are measured or that the temporal variations in various parts

4 of the spatial area are highly correlated. As discussed in Chapter 3, Sections 3.2.5 and 3A, a lack

5 of uniformity may lead to error due to low site-to-site correlations between daily concentrations

6 or to spatial differences in long-term average concentrations. The site-to-site correlation is most

7 important for acute epidemiologic studies that relate daily concentrations to daily health effects.

8 Data from the $PM_{2.5}$ monitoring network in 1999 and 2000 indicates relative high site-to-site

9 correlations in many cities. However, site-to-site correlations may not be as high for chemical

10 components or source category contributions. The small amount of data available suggest lower

11 site-to-site correlations for $PM_{10-2.5}$. In some cities, where PM air pollution is heavily influenced

12 by local point sources, site-to-site correlations of $PM_{2.5}$ may be low. Such cities may not provide

13 the best data for time-series epidemiology. Spatial differences in average concentration may be

14 more important for studies of the effects of long term exposure to PM on longevity or rates of

15 disease. Spatial inhomogeneity, as found in cities with local sources of primary $PM_{2.5}$, may be

16 more important for health effects that are nonlinear with PM dose in the range of PM dose

17 experienced.

18

19 *The Difference Between Ambient PM Concentration and Ambient PM Exposure*

20   As discussed in Chapter 5, Section 5.3, there are two sources of variability in the

21 relationship between ambient concentrations and exposure to ambient PM (also called ambient

22 PM exposure). The indoor environment is protective, in that the concentration of ambient PM

23 indoors is generally less than the concentration of ambient PM outdoors. The relationship

24 depends on the particle size and on the air exchange rate. Thus, there will be differences between

25 ultra fine, fine, and thoracic coarse PM and between air-conditioned and un-air-conditioned

26 homes. The second source of variability is the fraction of time spent outdoors. These two

27 sources of variability are combined into the attenuation factor, α, the ratio of ambient exposure to

28 ambient concentration. The product of α and the ambient PM concentration, C, yields the

29 ambient PM exposure, A (i.e., $A = \alpha C$) where α is different for the different particle-size

30 fractions. Since α may vary from person-to-person and time-to-time, due to variations in the air

31 exchange rate, the relationship between A and C may vary across the population and across

1   seasons. In spite of this variability, the correlation between *A* and *C* was high in the one study in

2   which individual daily values of *A* were estimated. Variations in α, as indexed by air

3   conditioning use, may explain some of the heterogeneity in excess rates of health effects

4   observed in epidemiologic studies of PM_{10} in different cities.

5

6   *Seasonal Variations*

7   Few epidemiological studies have had enough data for season-by-season analyses. Such

8   differences might be expected due to seasonal variations in the relative concentrations of

9   pollutants and PM components, the average α, correlations between ambient concentrations and

10   exposure, and correlations among potential surrogates and confounders. Most recent studies do

11   attempt to adjust for seasonal influences in their statistical models.

12

13   *The Difference Between Ambient PM Exposure and Total PM Exposure*

14   Total exposure to PM, as measured by a monitor worn by a person, is composed of an

15   ambient exposure component and a nonambient exposure component. The former includes

16   exposure to ambient pollution while outdoors and exposure to a fraction of the ambient pollution

17   while indoors. The latter is composed of primary and secondary indoor-generated PM and

18   personal cloud PM. The nonambient exposure is found to be variable from day-to-day for a

19   given subject and to be variable from subject-to-subject on a given day. However, the average

20   daily nonambient exposure may be relatively constant not only within a given city, but from city

21   to city within developed countries.

22

23   *Ambient Concentration—Personal Exposure Relationships for Gaseous Co-Pollutants*

24   Ambient concentrations of gaseous co-pollutants, such as CO, NO_2, SO_2 and O_3, are

25   sometimes used in epidemiologic analyses. Only a few studies have examined the correlations of

26   ambient copollutant concentrations with (1) ambient PM concentrations, (2) personal exposures

27   to co-pollutants, and (3) either ambient or total personal PM exposure. These studies find that

28   the ambient concentrations of NO_2, SO_2, and O_3 are not well correlated with personal exposure to

29   these gaseous co-pollutants. Rather, the concentrations of these gaseous co-pollutants and CO

30   are well correlated with the ambient concentrations of $PM_{2.5}$, the ambient exposures to $PM_{2.5}$, and

31   the total exposures to $PM_{2.5}$. Therefore, these studies conclude that ambient concentrations of

1   NO_2, SO_2, O_3, and likely CO, are not confounders but rather surrogates for ambient PM exposure

2   or more likely of ambient exposure to source categories with which the gases are correlated, i.e.,

3 NO_2 and CO with motor vehicle associated PM and SO_2 and O_3 with regional sulfate.

4

5   *The Difference Between Exposure and Dose*

6   As discussed in Chapter 6 there are several causes of variability between exposure and

7   dose. The relationship between exposure and dose is highly dependent on particle size. Not only

8   total deposition, but also the location of deposition, varies with particle size, as shown in

9   Figure 9-34. The deposition fraction and location also depends on the size of the lung and the

10   breathing rate and is different for nose breathing and mouth breathing. Thus, deposition is higher

11   during exercise than normal activity. Also, children, with smaller lungs and higher breathing

12   rates than adults, will have higher deposition fractions than adults. Deposition fraction and

13   deposition location may be different in people with compromised lungs. Very importantly,

14   deposition per unit surface area may be higher in the healthy sections of their lungs. It is not

15   currently known which of the various deposition parameters are most important, i.e., deposition

16   could be estimated as mass per body mass, particle surface area per lung surface area, or number

17   of particles per number of alveolar cells. The importance of exercise in influencing dose was

18   demonstrated in a recent study of asthma. Exposure to O_3 was related to increased prevalence of

19   asthma but only among children who participated in outdoor activities which involved exercise.

20

21   **9.13.2 Possible Errors Related to Health and Epidemiology**

22   *Resolution of Health Effects*

23   As of 2001, the majority of PM epidemiology data was based on the relationship between

24   PM_{10} mass and total mortality. However, it is possible that different kinds of particles may cause

25   different kinds of health effects and with different times between exposure and death. Thus,

26   lumping all nonaccidental deaths together may obscure useful information. Similar arguments

27   apply to morbidity. Some studies that consider classes of mortality tend to find higher excess

28   risks for cardiovascular and respiratory mortality than for total mortality.

29

30
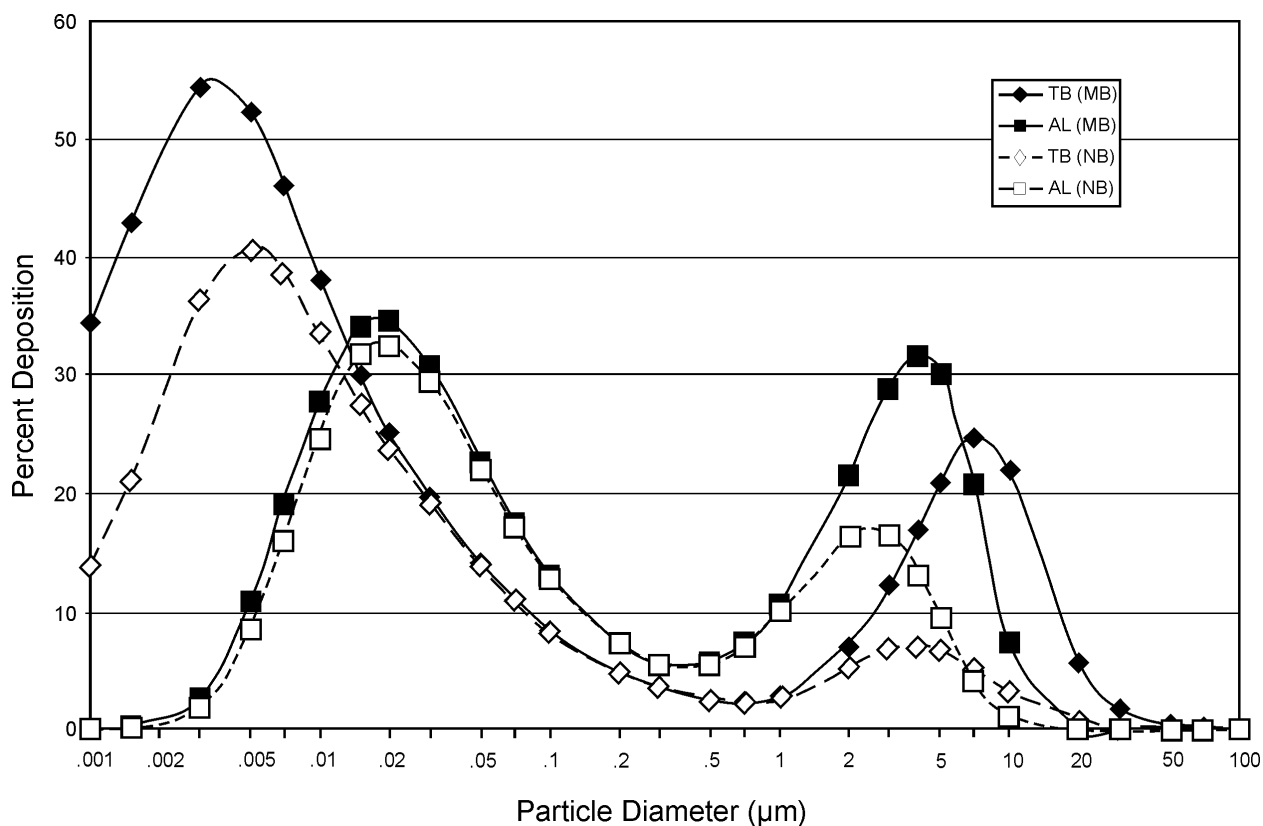
Figure 9-34. **The percent deposition of inhaled particles in the tracheobronchial (TB) and alveolar (A) regions of the lung as a function of particle size. The graph is based on calculations using the ICRP model for a young adult with an inhalation volume of 500 ml and a breathing frequency of 15 breaths a second for spherical particles with a density of 1 g/ce.**

1   *Variation in Time Between Exposure and Appearance of Health Effects*

2   Variations in toxicity of various types of PM or variations in the health status of members

3   of the exposed population may lead to variations in the time lag between exposure and

4   appearance of a response. Therefore, studies need to account for responses that may lag exposure

5   by several days. A dose of PM may also cause a health effect on more than one lag day. If so,

6   and if day to day concentrations are correlated, as is the usual case for PM, the use of only one

7   lag day will overestimate the risk on the lag day selected, due to autocorrelation, but will

8   underestimate the total risk. To obtain the total risk it is necessary to integrate the risk over

9   several days by a multiple regression model that accounts for health effects persisting for several

1 days. This technique, with either a constrained or unconstrained lag structure, or using a running

2 average of daily concentrations, accounts for autocorrelation in the day-to-day concentrations and

3 leads to higher estimated excess risks.

4

9.13.3 Apportioning Health Effects to PM (by size, chemical component, or source category) and Gaseous Co-Pollutants

7 One of the important technical problems in air pollution epidemiology is properly

8 apportioning health effects related to air pollution to the proper PM size fraction, chemical

9 component, or source component or to one or more gaseous co-pollutants. A major problem in

10 epidemiology is that a study may attribute an effect to a measured variable used as a regressor

11 when another measured or unmeasured variable is really the causal agent. The incorrect

12 attribution of effect (or part of the effect) to a variable used as a regressor, to another variable is

13 known as confounding. The potential for confounding exists anytime the concentration of a

14 causal agent is significantly correlated with the measured concentration of the regressor. The

15 proper apportionment of effect in air pollution epidemiology is difficult because PM and the

16 gaseous co-pollutants, NO_2, CO, SO_2, and O_3 are often significantly correlated with each other.

17 The concepts of confounding; over-, under-, and mis-filtering, and effects modification are

18 discussed in Sections 8.1 and 8.4. Consider the relationship diagramed in Figure 9-35 for two air

19 pollutants, A and B. Lines with double arrows indicate a statistically significant association

20 between the two variables. There are many possible variations in the relationships among these

21 variables.

22
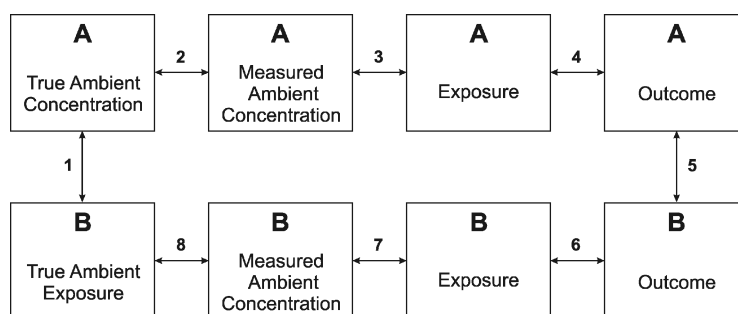
Figure 9-35. Diagram showing relationships (correlations) between A and B and between various concentration, exposure, and outcome measures.

1   1. All relationships, paths 1-8, are significant.

2   1a. In a multiple regression, A and B will share the health effects due to A and B. The

3   split will depend on the differential error in the paths between concentrations and outcomes.

4   Depending on the error structure and the relative strengths of the relationships, a portion of the

5   health effect due to the pollutant with the higher error will be transferred to the pollutant with

6   the lower error. It will not be possible to accurately apportion the health effects between A and B

7   (confounding).

8   1b. If A is used as a single regressor, some of the effect of A will be transferred to B and

9   the effect of A will be overestimated (A is confounded by B, under-fitting).

10

11   2. Pollutant A does not cause the outcome of interest at the exposure level encountered.

12   Pathways 4 and 5 and outcome A disappear.

13   2a. Using B as a single regressor, the correct value is obtained for the association of B with

14   the outcomes due to B.

15   2b. Using A as a single regressor, a false positive value is obtained for the effect of A due

16   to the correlation of A with B (A is a surrogate for B, mis-fitting).

17   2c. If A and B are used in a multiple regression, some of the effect of B will be transferred

18   to A and the true effect of B will be underestimated (over-fitting).

19

20   3. Pollutants A and B are independent and cause independent health effects. Pathways 1

21   and 5 disappear. Since the concentration-outcome relationships are independently, an analysis

22   with either single or multiple regressors will give the correct association for each pollutant.

23   Situation 3 is the desirable situation.

24

25   Unfortunately, it is not possible, on the basis of one epidemiologic study in one community

26   during one time period, to tell whether A or B is responsible for the health effects; or if both are

27   responsible, to correctly apportion the effects to each. To correctly apportion the health effects

28   between A and B it is necessary to seek other sources of information.

29

30   **Toxicity.** If we know that the potential confounder, A in situation 2, does not cause

31   outcome A at the levels of exposure, we know that a single regression with B as the regressor

1   will yield the correct value for the association of B with outcome B (Situation 2a). However, a

2   multiple regression using A and B would underestimate the association of outcome B with B

3   because some of the health effects due to B would be incorrectly transferred to A (Situation 2c,

4   over-fitting). Thus, if we know that A does not cause the outcome at the exposure level of A,

5   then the health effect may confidently be assigned to B (realizing that there could always be an

6   unknown variable C, correlated with B, that is really the causal agent).

7

8   **Exposure.** Useful information can also be obtained from concentration-exposure

9   relationships. Suppose that A and B are significantly correlated but that the ambient

10   concentration of A is not significantly correlated with either the ambient, nonambient, or total

11   personal exposure to A. This can occur, as discussed in Chapter 5 and Section 9.6.4, if the

12   spatial distribution of A is inhomogeneous of if A is very rapidly removed once it is penetrates

13   indoors. In this case pathway 4 disappears. Even is A is capable of causing the outcome at the

14   levels of exposure, a regression using A will not show any association because the exposure

15   causing the outcomes are not correlated with the concentration used as the regressor.

16

17   **Lag structure.** If the effect due to A peaks on the day of exposure (lag day 0) but the

18   effect of B peaks on the day after exposure (lag day 1), we can conclude that both A and B cause

19   independent effects. This conclusion holds only if the concentration of A is not correlated with

20   the concentration of B on the prior day.

21

22   **Multiple regression.** In a number of studies the effects attributed to A (β_A, the slope of the

23   regressions of A on outcomes) and B (β_B) in a multiple regression are compared to those in single

24   regressions to obtain information on possible confounding. An increase in the variance of β_A^M

25   and β_B^M, from the multiple regression, over those β_A^S and β_B^S, obtained from single regression; a

26   reduction in the values of either β_A^M and β_B^M compared to β_A^S and β_B^S, or a decrease in the value

27   of β for the combined action of A and B relative to sum of β_A^S and β_B^S is evidence for potential

28   confounding. However, this information is not sufficient to determine whether A is a confounder

29   of B or whether A is a surrogate for B. If, β_B^M equals β_B^S and $\beta_A^M = 0$, it may be assumed that B

30   is causal and A is not. In order for this to happen, the correlation between A and B would have

31   to be non-significant. Thus, if A and B are uncorrelated, β_A is zero or non-significant, and β_B is

1   positive and significant, a multiple regression, yielding similar values of β_A and β_B, will confirm

2   that A is noncausal and B is causal. If the correlation is between 0 and 1, the multiple regression

3   may provide some idea of how much of the effect of A could be due to potential confounding by

4   B, but it cannot determine whether the confounding is real or only potential. If a community is

5   studied where the correlation of A and B is low or nonsignificant, a comparison of single and

6   multiple regression can demonstrate that significant confounding is not occurring if that is the

7   case.

8

9   **Orthogonal regressors.** Various types of source apportion models have been developed to

10 assist implementation of PM standards by identifying the sources of PM in a given airshed. The

11 process involves application of statistical techniques such a factor analysis to daily concentration

12 values of PM components to generate orthogonal factors, containing various loadings of PM

13 components and in some cases, also containing gaseous co-pollutants. In some case, these

14 factors can be identified with specific source categories. This source category factor (SCF) can

15 be used to determine the daily contributions of these source factors to the PM concentration.

16 Since the SCF are orthogonal (i.e., independent and uncorrelated) we have situation 3 and either

17 single regressions with each source factor or a multiple regression with all SCF should give

18 correct values of the relationship of each SCF to the health outcomes with which it is related.

19 There will be no potential for confounding since the SCF are uncorrelated.

20   The concept of SCF can help explain some of the results from multiple regression of PM

21 and a gaseous co-pollutant. Consider the situation shown in Figure 9-36. The vehicular

22 traffic-related (VTR) SCF and the regional sulfate (RSO_4) SCF are uncorrelated and we will

23 assume they are causal. The VTR SCF contains contributions from CO, NO_2, and $PM_{2.5}$. The

24 RSO_4 SCF contain contributions from regional sulfate in the form of $(NH_4)_2SO_4$, $NH_4H_2SO_4$, and

25 H_2SO_4, but not local sulfate in the form of $CaSO_4$. $PM_{2.5}$ is correlated with both SCFs but CO

26 and NO_2 are only correlated with the VTR SCF.

27   Now considered a multiple regression using PM_{10} and CO (or NO_2) as variables. Since

28 $PM_{2.5}$ contains both RSO_4 and VTR components, it is possible that the ambient concentrations of

29 CO (or NO_2) will be more highly correlated than $PM_{2.5}$ with the ambient concentrations of the

30 VTR SCF. Thus, in a multiple regression, the effects of the VTR SCF would be transferred

31 largely to CO (or NO_2) and only the effects of RSO_4 would be transferred to the $PM_{2.5}$. Thus, CO
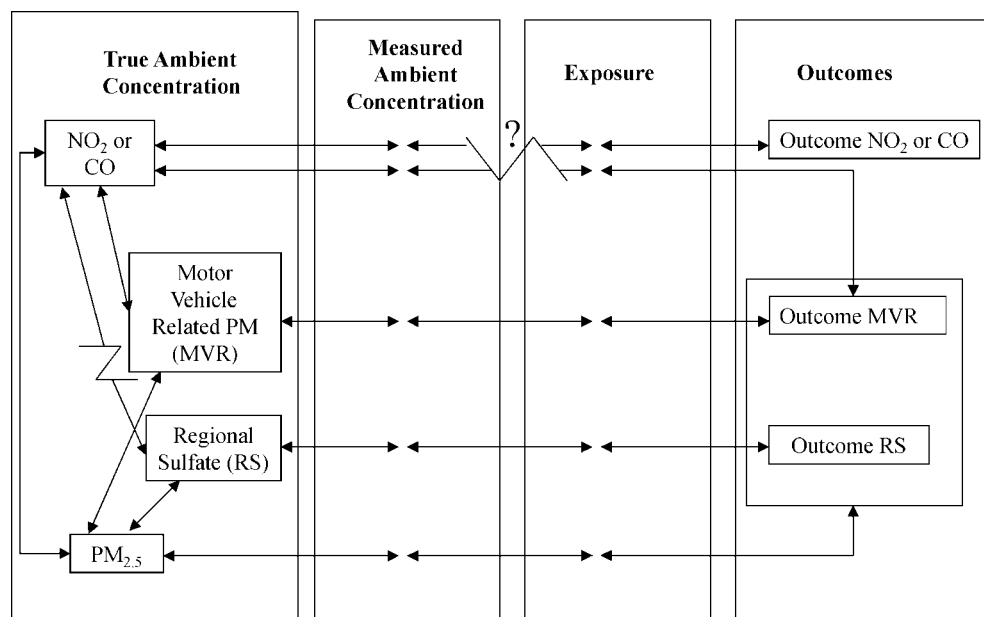
Figure 9-36. **Diagram showing concentrations—exposure—outcome relationships (correlations for CO or NO$_2$, PM$_{2.5}$, and source category factors for vehicular traffic related PM and regional sulfate.**

1   (or NO$_2$) might show a higher relative risk than PM$_{2.5}$ (or possibly than PM$_{2.5}$ in a single

2   regression) and the relative risk associated with PM$_{2.5}$ would be reduced in the multiple

3   regression. In this case, CO (or NO$_2$) would be confounded by the VTR SCF.

4   While a regression with SCFs will give excess risk values, unconfounded by other SCFs,

5   it will not be possible to tell from epidemiology alone whether the CO, the NO$_2$, or the PM

6   component of the VTR pollution is truly causal. However, in view of the anticipated low

7   correlation between CO and NO$_2$ with their respective personal exposures, and the unlikelihood

8   that CO or NO$_2$ cause acute mortality as the very low values of personal exposures for most of

9   the population, the identification of the PM component of VTR pollution as the most likely

10   causal agent is reasonable.

11

12

13

9.14 IMPLICATIONS OF HEALTH EFFECTS OF LONG-TERM EXPOSURES TO PARTICULATE MATTER

What are the implications of observed effects of long-term exposure to particulate matter and other pollutants for life expectancy?

9.14.1 Methodological Issues

Closed-cohort studies of ambient air pollutants are methodologically similar to typical epidemiological studies of occupational cohorts and, in some respects, to experimental trials. Subjects are enrolled, characterized as to their exposures and other relevant health factors, and followed over time as they experience adverse health outcomes. Methodological issues regarding the loss of subjects to follow-up, the movement of subjects between exposure groups or levels, and the characterization of exposure are well-understood and are adequately handled by standard epidemiologic methods.

The assignment of exposure in both environmental and occupational studies is generally based on area rather than personal sampling and any consequential exposure misclassification will generally bias effect estimates towards the null. With appropriate individual-level assessment and analysis of other risk factors, the assignment of a common exposure to a group does not give raise to an ecological fallacy (Kunzli and Tager, 1997). The current PM AQCD has avoided a reliance on purely ecological analyses of county-level data that lack individual-level data on non-environmental determinants of mortality.

A key difference between epidemiologic closed-cohorts studies and experimental trials is the lack of randomization of subjects to exposure. In observational studies, randomization is replaced by a careful consideration and analytic correction for differences in other salient health factors other than the exposure of interest. A potential confounder must be (a) an independent determinant of the outcome of interest among unexposed subjects, (b) non-causally associated with the exposure of interest, and (c) not a part of the causal pathway linking the exposure and outcome. Once these potential confounders have been controlled, differences in survival, that is, in the relative rates of mortality, are attributed to differences in subjects' exposure histories.

9.14.2 Overall Survival and Life Expectancy

Our current knowledge of the adverse health effects of long-term exposures to ambient particulate matter is based on a small number of epidemiological studies that compare differences in the survival of well-characterized closed-cohorts of free-living human subjects with air pollution levels in their cities of residence (AQCD Section 8.2.3). Compared with the more intricate methodological aspects of epidemiological studies of short-term particulate matter exposures using time-series methods to examine non-enumerated open-cohorts, the design, conduct and analysis of closed-cohorts is straightforward. However, such survival studies are much less common due to the difficulty and expense of enrolling and maintaining follow-up of an enumerated cohort.

At the time of the 1996 PM AQCD, three closed-cohort (survival) studies of particulate matter had been published in the peer-review literature. Two of these survival studies were national in scope, the Harvard Six-Cities Adult Cohort Study (Dockery et al., 1993) and the American Cancer Society Cohort Study (Pope et al., 1995), and one focused solely on California, the Adventist Health Study of Smog or AHSMOG (Abbey et al., 1991). The American Cancer Society Cohort Study was a secondary analysis of a very extensive cohort of 552,138 subjects in 151 cities whose exposures were characterized by routinely collected air quality data and who were followed for seven years. The Harvard Six-Cities Adult Cohort Study enrolled 8,111 subjects in six cities, characterized their exposures with investigator-conducted measurements of size-fractionated particulate matter, and followed these subjects for 14 to 16 years. The Adventist Health Study on Smog enrolled 6,340 non-smoking subjects, grouped into three major urban areas and the remainder of California, whose exposures were characterized by routinely collected air quality data, and who were followed for an average of 10 years.

The two national studies found strong associations between higher particulate matter levels and decreased survival. For non-external causes of mortality, a 25 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with increases in the rate of mortality: 36 percent in the Harvard Six-Cities Adult Study and 18 percent in the American Cancer Society Cohort Study. The California study did not initially find any statistically significant overall mortality effects.

After the 1996 PM AQCD was completed, concerns were expressed regarding the adequacy of the conduct and analysis of these survival studies of particulate matter (Gamble, 1998). Many

1   concerns related to standard methodological issues regarding the assessment of exposure,

2   geographic mobility, and adequacy of control for potential confounders.

3

9.14.3 Verification and Sensitivity Analyses

5   Since the 1996 PM AQCD, the two national studies have been critically reanalyzed by

6   independent researchers under the auspices of the Health Effects Institute (Krewski et al., 2000).

7   In addition to the replication and validation of the original findings of the Harvard Six-Cities

8   Adult Study, Krewski et al. considered the sensitivity of the original findings to alternative risk

9   models and analytic approaches. Generally this sensitivity analysis found that the original results

10   were robust to changes in model specification and the inclusion of other community-level

11   covariates. Both the original and the reanalyses found a 13% increase in risk of mortality per

12   10 μg/m^3 increment in PM$_{2.5}$. The HEI reanalysis project both confirmed and extended the

13   results of the American Cancer Society Cohort Study. Both the reanalysis and the extension

14   found a 7% increase in risk of mortality per 10 μg/m^3 in PM$_{2.5}$.

15   Since the conclusion of the reanalysis project, these three survival cohorts have been

16   extended by the original investigators to additional years of follow-up and alternative exposure

17   measures. Using airport visibility records to estimate exposures to PM$_{2.5}$, the Adventist Health

18   Study on Smog reported an 8.5 percent increase in the rate of non-external mortality associated

19   with a 10 μg/m^3 increment in PM$_{2.5}$ (McDonnell et al., 2000).

20   Thus, the relative risk estimates for these three survival cohorts have converged in the

21   range of 7 to 13 percent increase in the non-external mortality rate associated with a 10 μg/m^3

22   increment in a long-term average of PM$_{2.5}$. Methodological criticisms of these studies have been

23   largely resolved in favor of the validity of their original findings of a strong association between

24   long-term exposures to particulate matter and decreased survival (Bates, 2000).

25

9.14.4 Impact on Life-Expectancy

27   The increased rate of non-external mortality found in these three survival cohorts is greater

28   than the mere accumulation of the adverse effects of short-term exposures for a few days.

29   Conceptually, particulate matter may be associated with both the long-term development of

30   underlying health problems ("Frailty") and with the short-term variations in timing of mortality

1   among a susceptible population with some underlying health condition (Kunzli et al. 2001).

2   Epidemiologic studies of the mortality effects of short-term exposure to particulate matter using

3   unenumerated open-cohorts ("time-series studies") can only capture particulate matter's

4   association with short-term variations in mortality and, therefore, must systematically

5   underestimate the proportion of total mortality attributable to particulate matter. A recent

6   time-series study that examined the contribution of daily particulate matter levels over an

7   extended lag period (42 days) could only partially bridge the gap between the effects of

8   short-term and long-term exposures to particulate matter (Zanobetti et al., 2002).

9   Recent investigations of the public health implications of effect estimates for long-term PM

10   exposures also were reviewed in Chapter 8. Life table calculations by Brunekreef (1997) found

11   that relatively small differences in long-term exposure to airborne PM of ambient origin can have

12   substantial effects on life expectancy. For example, a calculation for the 1969 to 1971 life table

13   for U.S. white males indicated that a chronic exposure increase of 10 μg/m^3 PM was associated

14   with a reduction of 1.31 years for the entire population's life expectancy at age 25. The new

15   evidence noted above of infant mortality associations with PM exposure suggests that life

16   shortening in the entire population from long-term PM exposure could well be significantly

17   larger than estimated by Brunekreef (1997).

18

19   ## 9.14.5 Specific Causes of Death

20   The increase in non-external mortality cannot be explained by increases in chronic

21   respiratory diseases since chronic non-malignant lower respiratory disease accounts for only

22   5.6 percent and lung cancer for only another 6.9 percent of all deaths over age 24 years due to

23   non-external causes. Cardiovascular diseases, which account for 43 percent of non-external

24   mortality, must play the leading role in the decreased survival associated with exposure to

25   ambient PM. It is nevertheless useful to highlight the newer results of the extension of the ACS

26   study analyses (that include more years of participant follow-up and address previous criticisms

27   of the earlier ACS analyses), which provide the strongest evidence to date that long-term ambient

28   PM exposures are associated with increased risk of lung cancer. That increased risk appears to

29   be in about the same range as that seen for a non-smoker residing with a smoker and, therefore,

30   passively exposed chronically to tobacco smoke, with any consequent life-shortening impacts

31   due to lung cancer.

REFERENCES

Abbey, D. E.; Ostro, B. E.; Petersen, F.; Burchette, R. J. (1995) Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and other air pollutants. J. Exposure Anal. Environ. Epidemiol. 5: 137-159.

Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am. J. Respir. Crit. Care Med. 158: 289-298.

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Adams, P. F.; Hendershot, G. E.; Marano, M. A. (1999) Current estimates from the National Health Interview Survey, 1996. Vital Health Stat. 10(200).

Bigger, J. T., Jr.; Fleiss, J. L.; Steinman, R. C.; Rolnitzky, L. M.; Kleiger, R. E.; Rottman, J. N. (1992) Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 85: 164-171.

Bobak, M.; Leon, D. A. (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8. Occup. Environ. Med. 56: 539-543.

Broday, D. M.; Georgopoulos, P. G. (2000) Growth and deposition of hygroscopic particulate matter in the human lungs. Aerosol Sci. Technol.: submitted.

Brunekreef, B. (1997) Air pollution and life expectancy: is there a relation? Occup. Environ. Med. 54: 781-784.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.; Ozkaynak, H. (1998) The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manage. Assoc. 48: 689-700.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54: 130-139.

Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D. (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 15-39.

Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and mortality. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 61-72.

Chen, L.; Yang, W.; Jennison, B. L.; Omaye, S. T. (2000) Air particulate pollution and hospital admissions for chronic obstructive pulmonary disease in Reno, Nevada. Inhalation Toxicol. 12: 281-298.

Chock, D. P.; Winkler, S.; Chen, C. (2000) A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J. Air Waste Manage. Assoc. 50: 1481-1500.

Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM_{10} air pollution. Arch. Environ. Health 52: 113-117.

Cifuentes, L. A.; Vega, J.; Köpfer, K.; Lave, L. B. (2000) Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J. Air Waste Manage. Assoc. 50: 1287-1298.

Claiborn, C. S.; Finn, D.; Larson, T. V.; Koenig, J. Q. (2000) Windblown dust contributes to high $PM_{2.5}$ concentrations. J. Air Waste Manage. Assoc. 50: 1440-1445.

Clark, W. E.; Whitby, K. T. (1975) Measurements of aerosols produced by the photochemical oxidation of SO_2 in air. J. Colloid Interface Sci. 51: 477-490.

Clyde, M. A.; Guttorp, P.; Sullivan, E. (2000) Effects of ambient fine and coarse particles on mortality in Phoenix, Arizona. J. Exposure Anal. Environ. Epidemiol.: submitted.

Code of Federal Regulations. (1991a) Appendix J to Part 50–reference method for the determination of particulate matter as PM_{10} in the atmosphere. C. F. R. 40: §50.

Code of Federal Regulations. (1991b) Ambient air monitoring reference and equivalent methods. C. F. R. 40: §53.

Costa, D. L.; Dreher, K. L. (1999) What do we need to know about airborne particles to make effective risk management decisions? A toxicology perspective. Hum. Ecol. Risk Assess. 5: 481-491.

Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am. J. Epidemiol. 152: 397-406.

Dejmek, J.; Selevan, S. G.; Benes, I.; Solansky, I.; Srám, R. J. (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. Environ. Health Perspect. 107: 475-480.

Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H. (1998) Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. Environ. Health Perspect. 106: 751-761.

Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. Am. Rev. Respir. Dis. 139: 587-594.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect. 104: 500-505.

Dockery, D. W.; Pope, C. A., III; Kanner, R. E.; Villegas, G. M.; Schwartz, J. (1999) Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. Cambridge, MA: Health Effects Institute; research report no. 83.

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

Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 85-98.

Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ. Health Perspect. 107: 637-641.

Fanucchi, M. V.; Plopper, C. G. (1997) Pulmonary developmental responses to toxicants. In: Roth, R. A., ed. Toxicology of the Respiratory System, v. 8 of Comprehensive Toxicology. New York, NY: Pergamon, p. 203-220.

Fanucchi, M. V.; Wong, V. J.; Hinds, D.; Tarkington, B. K.; Van Winkle, L. S.; Evans, M. J.; Plopper, C. G. (2000) Repeated episodes of exposure to ozone alters postnatal development of distal conducting airways in infant rhesus monkeys. Am. J. Respir. Crit. Care Med. 161: A615.

Federal Register. (1987) Revisions to the national ambient air quality standards for particulate matter. F. R. (July 1) 52: 24,634-24,669.

Fitz-Simons, T. S.; Mathias, M.; Rizzo, M. (2000) Analyses of 1999 PM data for the PM NAAQS review. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; September 29.

Gardner, S. Y.; Lehmann, J. R.; Costa, D. L. (2000) Oil fly ash-induced elevation of plasma fibrinogen levels in rats. Toxicol. Sci. 56: 175-180.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Gielen, M. H.; Van Der Zee, S. C.; Van Wijnen, J. H.; Van Steen, C. J.; Brunekreef, B. (1997) Acute effects of summer air pollution on respiratory health of asthmatic children. Am. J. Respir. Crit. Care Med. 155: 2105-2108.

Gilmour, P. S.; Brown, D. M.; Lindsay, T. G.; Beswick, P. H.; MacNee, W.; Donaldson, K. (1996) Adverse health effects of PM_{10} particles: involvement of iron in generation of hydroxyl radical. Occup. Environ. Med. 53: 817-822.

Godleski, J. J.; Sioutas, C.; Katler, M.; Koutrakis, P. (1996) Death from inhalation of concentrated ambient air particles in animal models of pulmonary disease. Am. J. Respir. Crit. Care Med. 153: A15.

Godleski, J. J.; et al. (1998) Increased cardiac vulnerability during exposure to inhaled environmental particles [abstract]. Presented at: Health Effects Institute annual meeting; May; Boston, MA. Boston, MA: Health Effects Institute.

Godleski, J. J.; Verrier, R. L.; Koutrakis, P.; Catalano, P. (2000) Mechanisms of morbidity and mortality from exposure to ambient air particles. Cambridge, MA: Health Effects Institute; research report no. 91.

Gold, A.; Litonjua, J.; Schwartz, M.; Verrier, R.; Milstein, A.; Larson, E.; Lovett, B. (1998) Cardiovascular vulnerability to particulate pollution. Presented at: 1998 International conference [American Thoracic Society]; April; Chicago, IL. Am. J. Respir. Crit. Care Med. 157: A261.

Gold, D. R.; Damokosh, A. I.; Pope, C. A., III; Dockery, D. W.; McDonnell, W. F.; Serrano, P.; Retama, A.; Castillejos, M. (1999) Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. Epidemiology 10: 8-16.

Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. (2000) Ambient pollution and heart rate variability. Circulation 101: 1267-1273.

Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.; Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA: Health Effects Institute; research report 97. Available: http://www.healtheffects.org/pubs-research.htm [15 February, 2001].

Goldsmith, C.-A. W.; Hamada, K.; Ning, Y. Y.; Qin, G.; Catalano, P.; Murthy, G. G. K.; Lawrence, J.; Kobzik, L. (1999) The effects of environmental aerosols on airway hyperresponsiveness in a murine model of asthma. Inhalation Toxicol. 11: 981-998.

Gordon, T.; Nadziejko, C.; Chen, L. C.; Schlesinger, R. (2000) Effects of concentrated ambient particles in rats and hamsters: an exploratory study. Cambridge, MA: Health Effects Institute; research report no. 93.

Gwynn, R. C.; Burnett, R. T.; Thurston, G. D. (2000) A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ. Health Perspect. 108: 125-133.

Hayano, J.; Sakakibara, Y.; Yamada, M.; Ohte, N.; Fujinami, T.; Yokoyama, K.; Watanabe, Y.; Takata, K. (1990) Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. Circulation 81: 1217-1224.

Hofmann, W.; Balásházy, I.; Heistracher, T.; Koblinger, L. (1996) The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. Aerosol Sci. Technol. 25: 305-327.

Hoyert, D. L.; Kochanek, K. D.; Murphy, S. L. (1999) Deaths: final data for 1997. Atlanta, GA: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics. (National vital statistics reports: v. 47, no. 19).

Hsieh, T. H.; Yu, C. P. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhalation Toxicol. 10: 121-130.

Kamens, R.; Jang, M.; Chien, C.-J.; Leach, K. (1999) Aerosol formation from the reaction of α-pinene and ozone using a gas-phase kinetics-aerosol partitioning model. Environ. Sci. Technol. 33: 1430-1438.

Keywood, M. D.; Ayers, G. P.; Gras, J. L.; Gillett, R. W.; Cohen, D. D. (1999) Relationships between size segregated mass concentration data and ultrafine particle number concentrations in urban areas. Atmos. Environ. 33: 2907-2913.

Kim, Y. J.; Boatman, J. F.; Gunter, R. L.; Wellman, D. L.; Wilkison, S. W. (1993) Vertical distribution of atmospheric aerosol size distribution over south-central New Mexico. Atmos. Environ. Part A 27: 1351-1362.

Kittelson, D. B. (1998) Engines and nanoparticles: a review. J. Aerosol Sci. 29: 575-588.

Kleiger, R. E.; Miller, J. P.; Bigger J. T. Jr.; Moss, A. J.; Multicenter Post-infarction Research Group. (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am. J. Cardiol. 59: 256-262.

Kleinman, M. T.; Leaf, D. A.; Kelly, E.; Caiozzo, V.; Osann, K.; O'Niell, T. (1998) Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch. Environ. Health 53: 388-397.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling–interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. M., Jr.; Heilig, C. M.; Neas, L. M.; Dockery, D. W. (2000) Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. J. Air Waste Manage. Assoc. 50: 1215-1222.

Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. H.. (2000) Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.

Kuschner, W. G.; Wong, H.; D'Alessandro, A.; Quinlan, P.; Blanc, P. D. (1997) Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles. Environ. Health Perspect. 105: 1234-1237.

Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108: 941-947.

Lawrence, L.; Hall, M. J. (1999) 1997 summary: national hospital discharge survey. Hyattsville, MD: U.S. Department of Health & Human Resources, Centers for Disease Control and Prevention, National Center for Health Statistics. (Advance data from vital and health statistics: no. 308).

Layton, D. W. (1993) Metabolically consistent breathing rates for use in dose assessments. Health Phys. 64: 23-36.

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1997) *In vivo* and *in vitro* proinflammatory effects of particulate air pollution (PM_{10}). In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1279-1283.

Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. (1999) Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ. Health Perspect. 107: 521-525.

Linn, W. S.; Gong, H., Jr.; Shamoo, D. A.; Anderson, K. R.; Avol, E. L. (1997) Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. Arch. Environ. Health 52: 179-187.

Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ. Health Perspect. 108: 427-434.

Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000a) Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J. Air Waste Manage. Assoc.: 1501-1513.

Lipfert, F. W.; Zhang, J.; Wyzga, R. E. (2000b) Infant mortality and air pollution: a comprehensive analysis of U.S. data for 1990. J. Air Waste Manage. Assoc. 50: 1350-1366.

Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no. 95.

Loomis, D.; Castillejos, M.; Gold, D. R.; McDonnell, W.; Borja-Aburto, V. H. (1999) Air pollution and infant mortality in Mexico City. Epidemiology 10: 118-123.

Lumley, T.; Heagerty, P. (1999) Weighted empirical adaptive variance estimators for correlated data regression. J. R. Stat. Soc. B 61(part 2): 459-477.

Lundgren, D. A.; Burton, R. M. (1995) Effect of particle size distribution on the cut point between fine and coarse ambient mass fractions. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 131-148.

Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.

Martin, G. J.; Magid, N. M.; Myers, G.; Barnett, P. S.; Schaad, J. W.; Weiss, J. S.; Lesch, M.; Singer, D. H. (1987) Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. Am. J. Cardiol. 60: 86-89.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.; Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern California children with asthma. Environ. Health Perspect. 107: 757-760.

Michel, O.; Nagy, A.-M.; Schroeven, M.; Duchateau, J.; Nevè, J.; Fondu, P.; Sergysels, R. (1997) Dose-response relationship to inhaled endotoxin in normal subjects. Am. J. Respir. Crit. Care Med. 156: 1157-1164.

Monn, C.; Becker, S. (1999) Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine ($PM_{2.5}$) and coarse particles ($PM_{10-2.5}$) in outdoor and indoor air. Toxicol. Appl. Pharmacol. 155: 245-252.

Moolgavkar, S. H. (2000a) Air pollution and daily mortality in three U.S. counties. Environ. Health Perspect. 108: 777-784.

Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.

Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.

Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology 8: 364-370.

Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions for chronic respiratory disease in King County, Washington. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 157-171.

Morawska, L.; Thomas, S.; Bofinger, N.; Wainwright, D.; Neale, D. (1998) Comprehensive characterization of aerosols in a subtropical urban atmosphere: particle size distribution and correlation with gaseous pollutants. Atmos. Environ. 32: 2467-2478.

Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.

Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am. J. Public Health 85: 1361-1365.

Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999) Healthy women's PEF variations with ambient summer concentrations of PM_{10}, $PN_{2.5}$, SO_{42-}, H^+, and O_3. Am. J. Respir. Crit. Care Med. 160: 117-125.

Nakamura, T.; Hayashida, Y. (1992) Autonomic cardiovascular responses to smoke exposure in conscious rats. Am. J. Physiol. 262(5 pt. 2): R738-745.

National Institutes of Health. (1997) Guidelines for the diagnosis and management of asthma: expert panel report 2. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; publication no. 97-4051.

Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. Public Health Rep. 114: 135-148.

Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. Am. J. Epidemiol. 139: 1088-1099.

Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.

Neas, L. M.; Dockery, D. W.; Burge, H.; Koutrakis, P.; Speizer, F. E. (1996) Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. Am. J. Epidemiol. 143: 797-807.

Neas, L. M.; Schwartz, J.; Dockery, D. (1999) A case-crossover analysis of air pollution and mortality in Philadelphia. Environ. Health Perspect. 107: 629-631.

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

Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.

Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and stagnant air. Thorax 55: 466-470.

Ohtsuka, Y.; Clarke, R. W.; Mitzner, W.; Brunson, K.; Jakab, G. J.; Kleeberger, S. R. (2000) Interstrain variation in murine susceptibility to inhaled acid-coated particles. Am. J. Physiol. L469-L476.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Krupnick, A.; Harrington, W. (1993) Air pollution and respiratory morbidity among adults in Southern California. Am. J. Epidemiol. 137: 691-700.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.

Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, California: a follow-up study. J. Exposure Anal. Environ. Epidemiol. 10: 412-419.

Özkaynak, H.; Xue, J.; Zhou, H.; Raizenne, M. (1996) Associations between daily mortality and motor vehicle pollution in Toronto, Canada. Boston, MA: Harvard University School of Public Health, Department of Environmental Health; March 45.

Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ. Res. 74: 24-33.

Perry, K. D.; Cahill, T. A.; Eldred, R. A.; Dutcher, D. D.; Gill, T. E. (1997) Long-range transport of North African dust to the eastern United States. J. Geophys. Res. [Atmos] 102: 11,225-11,238.

Peters, A.; Döring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349: 1582-1587.

Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997b) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.

Peters, A.; Dockery, D. W.; Heinrich, J.; Wichmann, H. E. (1997c) Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur. Respir. J. 10: 872-879.

Peters, J. M.; Avol, E.; Navidi, W.; London, S. J.; Gauderman, W. J.; Lurmann, F.; Linn, W. S.; Margolis, H.; Rappaport, E.; Gong, H., Jr.; Thomas, D. C. (1999a) A study of twelve southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am. J. Respir. Crit. Care Med. 159: 760-767.

Peters, J. M.; Avol, E.; Gauderman, W. J.; Linn, W. S.; Navidi, W.; London, S. J.; Margolis, H.; Rappaport, E.; Vora, H.; Gong, H., Jr.; Thomas, D. C. (1999b) A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am. J. Respir. Crit. Care Med. 159: 768-775.

Plopper, C. G.; Fanucchi, M. V. (2000) Do urban environmental pollutants exacerbate childhood lung diseases? Environ. Health Perspect. 108: A252-A253.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999a) Particulate air pollution and daily mortality on Utah's Wasatch Front. Environ. Health Perspect.: 107: 567-573.

Pope, C. A.; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas, G. M.; Gold, D. R.; Dockery, D. W. (1999b) Heart rate variability associated with particulate air pollution. Am. Heart J. 138: 890-899.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect. 104: 506-514.

Ramadan, Z.; Song, X.-H.; Hopke, P. K. (2000) Identification of sources of Phoenix aerosol by positive matrix factorization. J. Air Waste Manage. Assoc. 50: 1308-1320.

Romieu, I.; Meneses, F.; Ruiz, S.; Sienra, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am. J. Respir. Crit. Care Med. 154: 300-307.

Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch. Environ. Health 52: 368-376.

Salvi, S.; Blomberg, A.; Rudell, B.; Kelly, F.; Sandström, T.; Holgate, S. T.; Frew, A. (1999) Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am. J. Respir. Crit. Care Med. 159: 702-709.

Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000a) National morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000b) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.

Sarnat, J. A.; Koutrakis, P.; Suh, H. H. (2000) Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J. Air Waste Manage. Assoc. 50: 1184-1198.

Schlesinger, R. B. (1988) Biological disposition of airborne particles: basic principles and application to vehicular emissions. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 239-298.

Schlesinger, R. B.; Ben-Jebria, A.; Dahl, A. R.; Snipes, M. B.; Ultman, J. (1997) Disposition of inhaled toxicants. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press; pp. 493-550.

Schwartz, J. (1997) Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377.

Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.

Schwartz, J. (2000) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151: 440-448.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology. 11: 6-10.

Schwartz, J.; Zanobetti, A. (2000) Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 11: 666-672.

Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.

Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc. 46: 927-939.

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.

Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.

Singer, D. H.; Martin, G. J.; Magid, N.; Weiss, J. S.; Schaad, J. W.; Kehoe, R.; Zheutlin, T.; Fintel, D. J.; Hsieh, A. M.; Lesch, M. (1988) Low heart rate variability and sudden cardiac death. J. Electrocardiol. 21(suppl.): S46-S55.

Smiley-Jewell, S. M.; Liu, F. J.; Weir, A. J.; Plopper, C. G. (2000) Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicol. Pathol. 28: 267-276.

Smith, R. L.; Spitzner, D.; Kim, Y.; Fuentes, M. (2000) Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. J. Air Waste Manage. Assoc. 50: 1367-1379.

Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol. 10: 461-477.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93: 1043-1065.

Terashima, T.; Wiggs, B.; English, D.; Hogg, J. C.; Van Eeden, S. F. (1997) Phagocytosis of small carbon particles (PM_{10}) by alveolar macrophages stimulates the release of polymorphonuclear leukocytes from bone marrow. Am. J. Respir. Crit. Care Med. 155: 1441-1447.

Thurston, G. D.; Ito, K.; Kinney, P. L.; Lippmann, M. (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. J. Exposure Anal. Environ. Epidemiol. 2: 429-450.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur. Respir. J. 13: 266-273.

Tolbert, P. E.; Klein, M.; Metzger, K. B.; Peel, J.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2000) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

Turpin, B. J. (1999) Options for characterizing organic particulate matter. Environ. Sci. Technol. 33: 76A-79A.

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

U.S. Environmental Protection Agency. (2000a) Air quality criteria for carbon monoxide. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available: www.epa.gov/ncea/co/ [2000, October 6].

U.S. Environmental Protection Agency. (2000b) Health assessment document for diesel exhaust [external review draft]. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-90/057E.

Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am. J. Respir. Crit. Care Med. 157: 1034-1043.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol. Sci. 41: 209-216.

Watkinson, W. P.; Campen, M. J.; Dreher, K. L.; Su, W.-Y.; Kodavanti, U.P.; Highfill, J. W.; Costa, D. L. (2000) Thermoregulatory effects following exposure to particulate matter in healthy and cardiopulmonary-compromised rats. J. Therm. Biol. 25: 131-137.

Weschler, C. J.; Shields, H. C. (1999) Indoor ozone/terpene reactions as a source of indoor particles. Atmos. Environ. 33: 2301-2312.

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

Whitby, K. T.; Sverdrup, G. M. (1980) California aerosols: their physical and chemical characteristics. In: Hidy, G. M.; Mueller, P. K.; Grosjean, D.; Appel, B. R.; Wesolowski, J. J., eds. The character and origins of smog aerosols: a digest of results from the California Aerosol Characterization Experiment (ACHEX). New York, NY: John Wiley & Sons, Inc.; pp. 477-517. (Advances in environmental science and technology: v. 9).

Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; Research Report no. 98.

Williams, R.; Suggs, J.; Zweidinger, R.; Evans, G.; Creason, J.; Kwok, R.; Rodes, C.; Lawless, P.; Sheldon, L. (2000a) The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 1. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. J. Exposure Anal. Environ. Epidemiol. 10: 518-532.

Williams, R.; Suggs, J.; Creason, J.; Rodes, C.; Lawless, P.; Kwok, R.; Zweidinger, R.; Sheldon, L. (2000b) The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. J. Exposure Anal. Environ. Epidemiol. 10: 533-543.

Williams, R. W.; Creason, J.; Zweidinger, R.; Watts, R. R.; Shy, C. (2000c) Indoor, outdoor, and personal exposure monitoring of particulate air pollution: the Baltimore elderly epidemiology-exposure pilot study. Atmos. Environ. 34: 4193-4204.

Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.

Woodruff, T. J.; Grillo, J.; Schoendorf, K. C. (1997) The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. Environ. Health Perspect. 105: 608-612.

Zanobetti, A.; Schwartz, J. (2000) Race, gender, and social status as modifiers of the effects of PM_{10} on mortality. J. Occup. Environ. Med. 42: 469-474.

Zhang, T.; Huang, C.; Johns, E. J. (1997) Neural regulation of kidney function by the somatosensory system in normotensive and hypertensive rats. Am. J. Physiol. 273: R1749-R1757.

Zhang, H.; Triche, E.; Leaderer, B. (2000) Model for the analysis of binary time series of respiratory symptoms. Am. J. Epidemiol. 151: 1206-1215.

APPENDIX 9A

Key Quantitative Estimates of Relative Risk for Particulate Matter-Related Health Effects Based on Epidemiologic Studies of U.S. and Canadian Cities Assessed in the 1996 Particulate Matter Air Quality Criteria Document

TABLE 9A-1. EFFECT ESTIMATES PER 50-μg/m^3 INCREASE IN 24-HOUR PM$_{10}$ CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR ($\pm$CI) Only PM in Model	RR ($\pm$CI) Other Pollutants in Model	Reported PM$_{10}$ Levels Mean (Min/Max)[†]
Increased Total Acute Mortality			
Six Cities[a]		—	
Portage, WI	1.04 (0.98, 1.09)	—	18 ($\pm$11.7)
Boston, MA	1.06 (1.04, 1.09)	—	24 ($\pm$12.8)
Topeka, KS	0.98 (0.90, 1.05)	—	27 ($\pm$16.1)
St. Louis, MO	1.03 (1.00, 1.05)	—	31 ($\pm$16.2)
Kingston/Knoxville, TN	1.05 (1.00, 1.09)	—	32 ($\pm$14.5)
Steubenville, OH	1.05 (1.00, 1.08)	—	46 ($\pm$32.3)
St. Louis, MO[c]	1.08 (1.01, 1.12)	1.06 (0.98, 1.15)	28 (1/97)
Kingston, TN[c]	1.09 (0.94, 1.25)	1.09 (0.94, 1.26	30 (4/67)
Chicago, IL[h]	1.04 (1.00, 1.08)	—	37 (4/365)
Chicago, IL[g]	1.03 (1.02, 1.04)	1.02 (1.01, 1.04)	38 (NR/128)
Utah Valley, UT[b]	1.08 (1.05, 1.11)	1.19 (0.96, 1.47)	47 (11/297)
Birmingham, AL[d]	1.05 (1.01, 1.10)	—	48 (21, 80)
Los Angeles, CA[f]	1.03 (1.00, 1.055)	1.02 (0.99, 1.036)	58(15/177)
Increased Hospital Admissions (for Elderly > 65 years)			
<u>Respiratory Disease</u>			
Toronto, Canada[i]	1.23 (1.02, 1.43)[‡]	1.12 (0.88, 1.36)[‡]	30-39[*]
Tacoma, WA[j]	1.10 (1.03, 1.17)	1.11 (1.02, 1.20)	37 (14, 67)
New Haven, CT[j]	1.06 (1.00, 1.13)	1.07 (1.01, 1.14)	41 (19, 67)
Cleveland, OH[k]	1.06 (1.00, 1.11)	—	43 (19, 72)
Spokane, WA[l]	1.08 (1.04, 1.14)	—	46 (16, 83)
<u>COPD</u>			
Minneapolis, MN[n]	1.25 (1.10, 1.44)	—	36 (18, 58)
Birmingham, AL[m]	1.13 (1.04, 1.22)	—	45 (19, 77)
Spokane, WA[l]	1.17 (1.08, 1.27)	—	46 (16, 83)
Detroit, MI[o]	1.10 (1.02, 1.17)	—	48 (22, 82)

TABLE 9A-1 (cont'd). EFFECT ESTIMATES PER 50-μg/m^3 INCREASE IN 24-HOUR PM$_{10}$ CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR ($\pm$CI) Only PM in Model	RR ($\pm$CI) Other Pollutants in Model	Reported PM$_{10}$ Levels Mean (Min/Max)[†]
Pneumonia			
Minneapolis, MN[n]	1.08 (1.01, 1.15)	—	36 (18,58)
Birmingham, AL[m]	1.09 (1.03, 1.15)	—	45 (19, 77)
Spokane, WA[l]	1.06 (0.98, 1.13)	—	46 (16, 83)
Detroit, MI[o]	—	1.06 (1.02, 1.10)	48 (22, 82)
Ischemic HD			
Detroit, MI[p]	1.02 (1.01, 1.03)	1.02 (1.00, 1.03)	48 (22, 82)
Increased Respiratory Symptoms			
Lower Respiratory			
Six Cities[q]	2.03 (1.36, 3.04)	Similar RR	30 (13,53)
Utah Valley, UT[r]	1.28 (1.06, 1.56)[τ]	—	46 (11/195)
	1.01 (0.81, 1.27)[π]		
Utah Valley, UT[s]	1.27 (1.08, 1.49)	—	76 (7/251)
Cough			
Denver, CO[x]	1.09 (0.57, 2.10)	—	22 (0.5/73)
Six Cities[q]	1.51 (1.12, 2.05)	Similar RR	30 (13, 53)
Utah Valley, UT[s]	1.29 (1.12, 1.48)	—	76 (7/251)
Decrease in Lung Function			
Utah Valley, UT[r]	55 (24, 86)[**]	—	46 (11/195)
Utah Valley, UT[s]	30 (10, 50)[**]	—	76 (7/251)
Utah Valley, UT[w]	29 (7,51)[***]	—	55 (1,181)

References:

[a]Schwartz et al. (1996a).
[b]Pope et al. (1992, 1994)/O$_3$.
[c]Dockery et al. (1992)/O$_3$.
[d]Schwartz (1993).
[g]Ito and Thurston (1996)/O$_3$.
[f]Kinney et al. (1995)/O$_3$, CO.
[h]Styer et al. (1995).
[i]Thurston et al. (1994)/O$_3$.
[j]Schwartz (1995)/SO$_2$.
[k]Schwartz et al. (1996b).

[l]Schwartz (1996).
[m]Schwartz (1994a).
[n]Schwartz (1994b).
[o]Schwartz (1994c).
[p]Schwartz and Morris (1995)/O$_3$, CO, SO$_2$.
[q]Schwartz et al. (1994).
[r]Pope et al. (1991).
[s]Pope and Dockery (1992).
[t]Schwartz (1994d).
[w]Pope and Kanner (1993).

[x]Ostro et al. (1991).
[†]Min/Max 24-h PM$_{10}$ in parentheses unless noted otherwise as standard deviation ($\pm$SD), 10 and 90 percentile (10, 90). NR = not reported.
[τ]Children.
[π]Asthmatic children and adults.
[*]Means of several cities.
[**]PEFR decrease in mL/s.
[***]FEV$_1$ decrease.
[‡]RR refers to total population, not just >65 years.

TABLE 9A-2. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES

Acute Mortality	Indicator	RR ($\pm$CI) per 25 $\mu g/m^3$ PM Increase	Reported PM Levels Mean (Min/Max)[†]
Six City[a]			
Portage, WI	$PM_{2.5}$	1.030 (0.993, 1.071)	11.2 ($\pm$7.8)
Topeka, KS	$PM_{2.5}$	1.020 (0.951, 1.092)	12.2 ($\pm$7.4)
Boston, MA	$PM_{2.5}$	1.056 (1.038, 1.0711)	15.7 ($\pm$9.2)
St. Louis, MO	$PM_{2.5}$	1.028 (1.010, 1.043)	18.7 ($\pm$10.5)
Kingston/Knoxville, TN	$PM_{2.5}$	1.035 (1.005, 1.066)	20.8 ($\pm$9.6)
Steubenville, OH	$PM_{2.5}$	1.025 (0.998, 1.053)	29.6 ($\pm$21.9)
Increased Hospitalization			
Ontario, Canada[b]	$SO_4^=$	1.03 (1.02, 1.04)	R = 3.1-8.2
Ontario, Canada[c]	$SO_4^=$	1.03 (1.02, 1.04)	R = 2.0-7.7
	O_3	1.03 (1.02, 1.05)	
NYC/Buffalo, NY[d]	$SO_4^=$	1.05 (1.01, 1.10)	NR
Toronto[d]	H^+ ($Nmol/m^3$)	1.16 (1.03, 1.30)[*]	28.8 (NR/391)
	$SO_4^=$	1.12 (1.00, 1.24)	7.6 (NR, 48.7)
	$PM_{2.5}$	1.15 (1.02, 1.78)	18.6 (NR, 66.0)
Increased Respiratory Symptoms			
Southern California[f]	$SO_4^=$	1.48 (1.14, 1.91)	R = 2-37
Six Cities[g]	$PM_{2.5}$	1.19 (1.01, 1.42)[**]	18.0 (7.2, 37)[***]
(Cough)	$PM_{2.5}$ Sulfur	1.23 (0.95, 1.59)[**]	2.5 (3.1, 61)[***]
	H^+	1.06 (0.87, 1.29)[**]	18.1 (0.8, 5.9)[***]
Six Cities[g]	$PM_{2.5}$	1.44 (1.15-1.82)[**]	18.0 (7.2, 37)[***]
(Lower Resp. Symp.)	$PM_{2.5}$ Sulfur	1.82 (1.28-2.59)[**]	2.5 (0.8, 5.9)[***]
	H^+	1.05 (0.25-1.30)[**]	18.1 (3.1, 61)[***]
Decreased Lung Function			
Uniontown, PA[e]	$PM_{2.5}$	PEFR 23.1 (-0.3, 36.9) (per 25 $\mu g/m^3$)	25/88 (NR/88)

References:

[a]Schwartz et al. (1996a).
[b]Burnett et al. (1994).
[c]Burnett et al. (1995) O_3.
[d]Thurston et al. (1992, 1994).
[d]Neas et al. (1995).
[f]Ostro et al. (1993).
[g]Schwartz et al. (1994).

[†]Min/Max 24-h PM indicator level shown in parentheses unless otherwise noted as ($\pm$SD), 10 and 90 percentile (10,90) or R = range of values from min-max, no mean value reported.
[*]Change per 100 nmoles/m^3
[**]Change per 20 $\mu g/m^3$ for $PM_{2.5}$; per 5 $\mu g/m^3$ for $PM_{2.5}$ sulfur; per 25 nmoles/m^3 for H^+.
[***]50th percentile value (10,90 percentile).

TABLE 9A-3. EFFECT ESTIMATES PER INCREMENTS[a] IN ANNUAL MEAN LEVELS OF FINE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels Means ($\mu g/m^3$)
Increased Total Chronic Mortality in Adults		Relative Risk (95% CI)	
Six City[b]	$PM_{15/10}$	1.42 (1.16-2.01)	18-47
	$PM_{2.5}$	1.31 (1.11-1.68)	11-30
	$SO_4^=$	1.46 (1.16-2.16)	5-13
ACS Study[c] (151 U.S. SMSA)	$PM_{2.5}$	1.17 (1.09-1.26)	9-34
	$SO_4^=$	1.10 (1.06-1.16)	4-24
Increased Bronchitis in Children		Odds Ratio (95% CI)	
Six City[d]	$PM_{15/10}$	3.26 (1.13, 10.28)	20-59
Six City[e]	TSP	2.80 (1.17, 7.03)	39-114
24 City[f]	H^+	2.65 (1.22, 5.74)	6.2-41.0
24 City[f]	$SO_4^=$	3.02 (1.28, 7.03)	18.1-67.3
24 City[f]	$PM_{2.1}$	1.97 (0.85, 4.51)	9.1-17.3
24 City[f]	PM_{10}	3.29 (0.81, 13.62)	22.0-28.6
Southern California[g]	$SO_4^=$	1.39 (0.99, 1.92)	—
Decreased Lung Function in Children			
Six City[d,h]	$PM_{15/10}$	NS Changes	20-59
Six City[e]	TSP	NS Changes	39-114
24 City[i,j]	H^+ (52 nmoles/m^3)	−3.45% (-4.87, -2.01) FVC	—
24 City[i]	$PM_{2.1}$ (15 $\mu g/m^3$)	−3.21% (-4.98, -1.41) FVC	—
24 City[i]	$SO_4^=$ (7 $\mu g/m^3$)	−3.06% (-4.50, -1.60) FVC	—
24 City[i]	PM_{10} (17 $\mu g/m^3$)	−2.42% (-4.30, -.51) FVC	—

[a]Estimates calculated annual-average PM increments assume: a 100-$\mu g/m^3$ increase for TSP; a 50-$\mu g/m^3$ increase for PM_{10} and PM_{15}; a 25-$\mu g/m^3$ increase for $PM_{2.5}$; and a 15-$\mu g/m^3$ increase for $SO_4^=$, except where noted otherwise; a 100-nmole/m^3 increase for H^+.
[b]Dockery et al. (1993).
[c]Pope et al. (1995).
[d]Dockery et al. (1989).
[e]Ware et al. (1986).
[f]Dockery et al. (1996).
[g]Abbey et al. (1995).
[h]NS Changes = No significant changes.
[i]Raizenne et al. (1996).
[j]Pollutant data same as for Dockery et al. (1996).

REFERENCES

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995b) Estimating fine particulates less that 2.5 microns in aerodynamic diameter (PM2.5) from airport visibility data in California. J. Exposure Anal. Environ. Epidemiol. 5: 161-180.

Abbey, D. E.; Ostro, B. E.; Petersen, F.; Burchette, R. J. (1995c) Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and other air pollutants. J. Exposure Anal. Environ. Epidemiol. 5: 137-159.

Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am. J. Respir. Crit. Care Med. 158: 289-298.

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Adams, P. F.; Hendershot, G. E.; Marano, M. A. (1999) Current estimates from the National Health Interview Survey, 1996. Vital Health Stat. 10(200).

American Conference of Governmental Industrial Hygienists. (1994) Appendix D: particle size-selective sampling criteria for airborne particulate matter. In: 1994-1995 Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; pp. 43-46.

Bates, D. V. (2000) Lines that connect: assessing the causality inference in the case of particulate pollution. Environ. Health Perspect. 108: 91-92.

Becker, S.; Soukup, J. M.; Gilmour, M. I.; Devlin, R. B. (1996) Stimulation of human and rat alveolar macrophages by urban air particulates: effects on oxidant radical generation and cytokine production. Toxicol. Appl. Pharmacol. 141: 637-648.

Berglund, D. J.; Abbey, D. E.; Lebowitz, M. D.; Knutsen, S. F.; McDonnell, W. F. (1999) Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest 115: 49-59.

Binková, B.; Veselý, D.; Veselá, D.; Jelínek, R.; Šrám, R. J. (1999) Genetoxicity and embryotoxicity of urban air particulate matter collected during winter and summer period in two different districts of the Czech Republic. Mutat. Res. 440: 45-58.

Bobak, M.; Leon, D. A. (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8. Occup. Environ. Med. 56: 539-543.

Brook, R. D.; Brook, J. R.; Urch, B.; Vincent, R.; Rajagopalan, S.; Silverman, F. (2002) Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in health adults. Circulation 105: 1534-1536.

Brunekreef, B. (1997) Air pollution and life expectancy: is there a relation? Occup. Environ. Med. 54: 781-784.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.; Ozkaynak, H. (1998) The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manage. Assoc. 48: 689-700.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54: 130-139.

Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D. (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 15-39.

Calvert, J. G.; Heywood, J. B.; Sawyer, R. F.; Seinfeld, J. H. (1993) Achieving acceptable air quality: some reflections on controlling vehicle emissions. Science (Washington, DC) 261: 37-45.

Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and mortality. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 61-72.

Chapman, R. S.; Watkinson, W. P.; Dreher, K. L.; Costa, D. L. (1997) Ambient particulate matter and respiratory and cardiovascular illness in adults: particle-borne transition metals and the heart-lung axis. Environ. Toxicol. Pharmacol. 4: 331-338.

Chen, L.; Yang, W.; Jennison, B. L.; Omaye, S. T. (2000) Air particulate pollution and hospital admissions for chronic obstructive pulmonary disease in Reno, Nevada. Inhalation Toxicol. 12: 281-298.

Chock, D. P.; Winkler, S.; Chen, C. (2000) A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J. Air Waste Manage. Assoc. 50: 1481-1500.

Chorąży, M.; Szeliga, J.; Stróżyk, M.; Cimander, B. (1994) Ambient air pollutants in Upper Silesia: partial chemical composition and biological activity. In: Symposium of risk assessment of urban air: emissions, exposure, risk identification, and risk quantitation; May-June 1992; Stockholm, Sweden. Environ. Health Perspect. 102(suppl 4): 61-66.

Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM_{10} air pollution. Arch. Environ. Health 52: 113-117.

Cifuentes, L. A.; Vega, J.; Köpfer, K.; Lave, L. B. (2000) Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J. Air Waste Manage. Assoc. 50: 1287-1298.

Claiborn, C. S.; Finn, D.; Larson, T. V.; Koenig, J. Q. (2000) Windblown dust contributes to high $PM_{2.5}$ concentrations. J. Air Waste Manage. Assoc. 50: 1440-1445.

Clarke, R. W.; Antonini, J. M.; Hemenway, D. R.; Frank, R.; Kleeberger, S. R.; Jakab, G. J. (2000) Inhaled particle-bound sulfate: effects on pulmonary inflammatory responses and alveolar macrophage function. Inhalation Toxicol. 12: 169-186.

Clyde, M. A.; Guttorp, P.; Sullivan, E. (2000) Effects of ambient fine and coarse particles on mortality in Phoenix, Arizona. J. Exposure Anal. Environ. Epidemiol.: submitted.

Code of Federal Regulations. (2001a) Appendix J to Part 50--reference method for the determination of particulate matter as PM10 in the atmosphere. C. F. R. 40: §50.

Code of Federal Regulations. (2001b) Appendix L to Part 50--reference method for the determination of fine particulate matter as PM2.5 in the atmosphere. C. F. R. 40: §50.

Costa, D. L.; Dreher, K. L. (1999) What do we need to know about airborne particles to make effective risk management decisions? A toxicology perspective. Hum. Ecol. Risk Assess. 5: 481-491.

Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am. J. Epidemiol. 152: 397-406.

Dejmek, J.; Selevan, S. G.; Benes, I.; Solansky, I.; Srám, R. J. (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. Environ. Health Perspect. 107: 475-480.

Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H. (1998) Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. Environ. Health Perspect. 106: 751-761.

Dockery, D. W.; Spengler, J. D. (1981) Personal exposure to respirable particulates and sulfates. J. Air Pollut. Control Assoc. 31: 153-159.

Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. Am. Rev. Respir. Dis. 139: 587-594.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect. 104: 500-505.

Dockery, D. W.; Pope, C. A., III; Kanner, R. E.; Villegas, G. M.; Schwartz, J. (1999) Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. Cambridge, MA: Health Effects Institute; research report no. 83.

Dong, W.; Lewtas, J.; Luster, M. I. (1996) Role of endotoxin in tumor necrosis factor "alpha" expression from alveolar macrophages treated with urban air particles. Exp. Lung Res. 22: 577-592.

Dreher, K. L. (2000) Particulate matter physicochemistry and toxicology: in search of causality—a critical perspective. Inhalation Toxicol. 12(suppl. 3): 45-57.

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

Dye, J. A.; Lehmann, J. R.; McGee, J. K.; Winsett, D. W.; Ledbetter, A. D.; Everitt, J. I.; Ghio, A. J.; Costa, D. L. (2001) Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ. Health Perspect. 109(suppl. 3): 395-403.

Ebelt, S. T.; Petkau, A. J.; Vedal, S.; Fisher, T. V.; Brauer, M. (2000) Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. J. Air Waste Manage. Assoc. 50: 1081-1094.

Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 85-98.

Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ. Health Perspect. 107: 637-641.

Fanucchi, M. V.; Wong, V. J.; Hinds, D.; Tarkington, B. K.; Van Winkle, L. S.; Evans, M. J.; Plopper, C. G. (2000) Repeated episodes of exposure to ozone alters postnatal development of distal conducting airways in infant rhesus monkeys. Am. J. Respir. Crit. Care Med. 161: A615.

Federal Register. (1987) Revisions to the national ambient air quality standards for particulate matter. F. R. (July 1) 52: 24,634-24,669.

Federal Register. (1997) National ambient air quality standards for particulate matter; final rule. F. R. (July 18) 62: 38,652-38,752.

Fitz-Simons, T. S.; Mathias, M.; Rizzo, M. (2000) Analyses of 1999 PM data for the PM NAAQS review. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; September 29.

Fortoul, T. I.; Osorio, L. S.; Tovar, A. T.; Salazar, D.; Castilla, M. E.; Olaiz-Fernández, G. (1996) Metals in lung tissue from autopsy cases in Mexico City residents: comparison of cases from the 1950s and the 1980s. Environ. Health Perspect. 104: 630-632.

Frampton, M. W.; Ghio, A. J.; Samet, J. M.; Carson, J. L.; Carter, J. D.; Devlin, R. B. (1999) Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. Am. J. Physiol. 277: L960-L967.

Gamble, J. L. (1998) Effects of ambient air pollution on daily mortality: a time series analysis of Dallas, Texas, 1990-1994. Presented at: 91st annual meeting and exhibition of the Air & Waste Management Association; June; San Diego, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 98-MP26.03.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Ghio, A. J.; Devlin, R. B. (2001) Inflammatory lung injury after bronchial instillation of air pollution particles. Am. J. Respir. Crit. Care Med. 164: 704-708.

Ghio, A. J.; Kim, C.; Devlin, R. B. (2000) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am. J. Respir. Crit. Care Med. 162: 981-988.

Ghio, A. J.; Gilbey, J. G.; Roggli, V. L.; Richards, J. H.; McGee, J. K.; Carson, J. L.; Devlin, R. B.; Cascio, W. E. (2001) Diffuse alveolar damage after exposure to an oil fly ash. Am. J. Respir. Crit. Care Med. 164: 1514-1518.

Gielen, M. H.; Van Der Zee, S. C.; Van Wijnen, J. H.; Van Steen, C. J.; Brunekreef, B. (1997) Acute effects of summer air pollution on respiratory health of asthmatic children. Am. J. Respir. Crit. Care Med. 155: 2105-2108.

Godleski, J. J.; Sioutas, C.; Katler, M.; Koutrakis, P. (1996) Death from inhalation of concentrated ambient air particles in animal models of pulmonary disease. Am. J. Respir. Crit. Care Med. 153: A15.

Gold, D. R.; Damokosh, A. I.; Pope, C. A., III; Dockery, D. W.; McDonnell, W. F.; Serrano, P.; Retama, A.; Castillejos, M. (1999) Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. Epidemiology 10: 8-16.

Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. (2000) Ambient pollution and heart rate variability. Circulation 101: 1267-1273.

Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.; Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA: Health Effects Institute; research report 97. Available: http://www.healtheffects.org/pubs-research.htm [15 February, 2001].

Guenther, A.; Geron, C.; Pierce, T.; Lamb, B.; Harley, P.; Fall, R. (2000) Natural emissions of non-methane volatile organic compounds, carbon monoxide, and oxides of nitrogen from North America. Atmos. Environ. 34: 2205-2230.

Gwynn, R. C.; Burnett, R. T.; Thurston, G. D. (2000) A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ. Health Perspect. 108: 125-133.

Henry, R. C. (1997) History and fundamentals of multivariate air quality receptor models. Chemom. Intell. Lab. Syst. 37: 37-42.

Hofmann, W.; Balásházy, I.; Heistracher, T.; Koblinger, L. (1996) The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. Aerosol Sci. Technol. 25: 305-327.

Hoyert, D. L.; Kochanek, K. D.; Murphy, S. L. (1999) Deaths: final data for 1997. Atlanta, GA: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics. (National vital statistics reports: v. 47, no. 19).

Hsieh, T. H.; Yu, C. P. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhalation Toxicol. 10: 121-130.

Imrich, A.; Ning, Y. Y.; Koziel, H.; Coull, B.; Kobzik, L. (1999) Lipopolysaccharide priming amplifies lung macrophage tumor necrosis factor production in response to air particles. Toxicol. Appl. Pharmacol. 159: 117-124.

Izzotti, A.; Camoirano, A.; DAgostini, F.; Sciacca, S.; De Naro Papa, F.; Cesarone, C. F.; De Flora, S. (1996) Biomarker alterations produced in rat lung by intratracheal instillations of air particulate extracts and chemoprevention with oral N-acetylcysteine. Cancer Res. 56: 1533-1538.

Jakab, G. J.; Clarke, R. W.; Hemenway, D. R.; Longphre, M. V.; Kleeberger, S. R.; Frank, R. (1996) Inhalation of acid coated carbon black particles impairs alveolar macrophage phagocytosis. Toxicol. Lett. 88: 243-248.

Janssen, N. A. H.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as modifiers of the effect of PM10 on hospital admissions for heart and lung disease. Environ. Health Perspect. 110: 43-49.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling–interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. M., Jr.; Heilig, C. M.; Neas, L. M.; Dockery, D. W. (2000) Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. J. Air Waste Manage. Assoc. 50: 1215-1222.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Watkinson, W. P.; Campen, M. J.; Winsett, D. W.; Richards, J. R.; Crissman, K. M.; Hatch, G. E.; Costa, D. L. (2000) The spontaneously hypertensive rat as a model of human cardiovascular disease: evidence of exacerbated cardiopulmonary injury and oxidative stress from inhaled emission particulate matter. Toxicol. Appl. Pharmacol. 164: 250-263.

Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. H.. (2000) Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.

Künzli, N.; Tager, I. B. (1997) The semi-individual study in air pollution epidemiology: a valid design as compared to ecologic studies. Environ. Health Perspect. 105: 1078-1083.

Künzli, N.; Medina, S.; Kaiser, R.; Quénel, P.; Horak, F., Jr.; Studnicka, M. (2001) Assessment of deaths attributable to air pollution: should we use risk estimates based on time series or on cohort studies? Am. J. Epidemiol. 153: 1050-1055.

Kuschner, W. G.; Wong, H.; D'Alessandro, A.; Quinlan, P.; Blanc, P. D. (1997) Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles. Environ. Health Perspect. 105: 1234-1237.

Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108: 941-947.

Lambert, A. L.; Dong, W.; Selgrade, M. K.; Gilmour, M. I. (2000) Enhanced allergic sensitization by residual oil fly ash particles is mediated by soluble metal constituents. Toxicol. Appl. Pharmacol. 165: 84-93.

Landis, M. S.; Norris, G. A.; Williams, R. W.; Weinstein, J. P. (2001) Personal exposures to $PM_{2.5}$ mass and trace elements in Baltimore, MD, USA. Atmos. Environ. 35: 6511-6524.

Lawrence, L.; Hall, M. J. (1999) 1997 summary: national hospital discharge survey. Hyattsville, MD: U.S. Department of Health & Human Resources, Centers for Disease Control and Prevention, National Center for Health Statistics. (Advance data from vital and health statistics: no. 308).

Layton, D. W. (1993) Metabolically consistent breathing rates for use in dose assessments. Health Phys. 64: 23-36.

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1997) *In vivo* and *in vitro* proinflammatory effects of particulate air pollution (PM_{10}). In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1279-1283.

Li, X. Y.; Brown, D.; Smith, S.; MacNee, W.; Donaldson, K. (1999) Short-term inflammatory responses following intratracheal instillation of fine and ultrafine carbon black in rats. Inhalation Toxicol. 11: 709-731.

Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. (1999) Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ. Health Perspect. 107: 521-525.

Linn, W. S.; Gong, H., Jr.; Shamoo, D. A.; Anderson, K. R.; Avol, E. L. (1997) Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. Arch. Environ. Health 52: 179-187.

Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ. Health Perspect. 108: 427-434.

Lioy, P. J. (1990) Assessing total human exposure to contaminants: a multidisciplinary approach. Environ. Sci. Technol. 24: 938-945.

Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000a) Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J. Air Waste Manage. Assoc.: 1501-1513.

Lipfert, F. W.; Zhang, J.; Wyzga, R. E. (2000b) Infant mortality and air pollution: a comprehensive analysis of U.S. data for 1990. J. Air Waste Manage. Assoc. 50: 1350-1366.

Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no. 95.

Lison, D.; Lardot, C.; Huaux, F.; Zanetti, G.; Fubini, B. (1997) Influence of particle surface area on the toxicity of insoluble manganese dioxide dusts. Arch. Toxicol. 71: 725-729.

Long, C. M.; Suh, H. H.; Koutrakis, P. (2000) Characterization of indoor particle sources using continuous mass and size monitors. J. Air Waste Manage. Assoc. 50: 1236-1250.

Loomis, D.; Castillejos, M.; Gold, D. R.; McDonnell, W.; Borja-Aburto, V. H. (1999) Air pollution and infant mortality in Mexico City. Epidemiology 10: 118-123.

Lumley, T.; Heagerty, P. (1999) Weighted empirical adaptive variance estimators for correlated data regression. J. R. Stat. Soc. B 61(part 2): 459-477.

Lundgren, D. A.; Burton, R. M. (1995) Effect of particle size distribution on the cut point between fine and coarse ambient mass fractions. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 131-148.

Mage, D.; Wilson, W.; Hasselblad, V.; Grant, L. (1999) Assessment of human exposure to ambient particulate matter. J. Air Waste Manage. Assoc. 49: 174-185.

Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.; Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern California children with asthma. Environ. Health Perspect. 107: 757-760.

McDonnell, W. F.; Nishino-Ishikawa, N.; Petersen, F. F.; Chen, L. H.; Abbey, D. E. (2000) Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J. Exposure Anal. Environ. Epidemiol. 10: 427-436.

Michel, O.; Nagy, A.-M.; Schroeven, M.; Duchateau, J.; Nevè, J.; Fondu, P.; Sergysels, R. (1997) Dose-response relationship to inhaled endotoxin in normal subjects. Am. J. Respir. Crit. Care Med. 156: 1157-1164.

Monn, C. (2001) Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmos. Environ. 35: 1-32.

Monn, C.; Becker, S. (1999) Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine ($PM_{2.5}$) and coarse particles ($PM_{10-2.5}$) in outdoor and indoor air. Toxicol. Appl. Pharmacol. 155: 245-252.

Moolgavkar, S. H. (2000a) Air pollution and daily mortality in three U.S. counties. Environ. Health Perspect. 108: 777-784.

Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.

Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.

Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology 8: 364-370.

Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions for chronic respiratory disease in King County, Washington. In: Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicology 12(suppl. 1): 157-171.

Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.

Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999) Healthy women's PEF variations with ambient summer concentrations of PM_{10}, $PN_{2.5}$, SO_{42-}, H^+, and O_3. Am. J. Respir. Crit. Care Med. 160: 117-125.

NARSTO. (2002) Fine particle assessment (2nd review draft). Available: http://www.cgenv.com/Narsto/ (13 February 2002).

National Institutes of Health. (1997) Guidelines for the diagnosis and management of asthma: expert panel report 2. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; publication no. 97-4051.

National Research Council. (1983) Acid deposition: atmospheric processes in eastern North America, a review of current scientific understanding. Washington, DC: National Academy Press.

National Research Council. (1994) Science and judgment in risk assessment. Washington, DC: National Academy Press.

National Research Council. (1998) Research priorities for airborne particulate matter. I. Immediate priorities and a long-range research portfolio. Washington, DC: National Academy Press.

National Research Council. (2001) Research priorities for airborne particulate matter. III. Early research progress. Washington, DC: National Academy Press. Available: http://www.nap.edu/catalog/10065.html [30 April, 2002].

Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. Public Health Rep. 114: 135-148.

Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. Am. J. Epidemiol. 139: 1088-1099.

Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.

Neas, L. M.; Dockery, D. W.; Burge, H.; Koutrakis, P.; Speizer, F. E. (1996) Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. Am. J. Epidemiol. 143: 797-807.

Neas, L. M.; Schwartz, J.; Dockery, D. (1999) A case-crossover analysis of air pollution and mortality in Philadelphia. Environ. Health Perspect. 107: 629-631.

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

Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.

Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and stagnant air. Thorax 55: 466-470.

Oberdörster, G.; Ferin, J.; Lehnert, B. E. (1994) Correlation between particle size, *in vivo* particle persistence, and lung injury. Environ. Health Perspect. 102(suppl. 5): 173-179.

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

Ostro, B. (1995) Fine particulate air pollution and mortality in two Southern California counties. Environ. Res. 70: 98-104.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Krupnick, A.; Harrington, W. (1993) Air pollution and respiratory morbidity among adults in Southern California. Am. J. Epidemiol. 137: 691-700.

Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, California: a follow-up study. J. Exposure Anal. Environ. Epidemiol. 10: 412-419.

Ott, W.; Wallace, L.; Mage, D. (2000) Predicting particulate (PM_{10}) personal exposure distributions using a random component superposition statistical model. J. Air Waste Manage. Assoc. 50: 1390-1406.

Özkaynak, H.; Xue, J.; Zhou, H.; Raizenne, M. (1996) Associations between daily mortality and motor vehicle pollution in Toronto, Canada. Boston, MA: Harvard University School of Public Health, Department of Environmental Health; March 45.

Patterson, E.; Eatough, D. J. (2000) Indoor/outdoor relationships for ambient $PM_{2.5}$ and associated pollutants: epidemiological implications in Lindon, Utah. J. Air Waste Manage. Assoc. 50: 103-110.

Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ. Res. 74: 24-33.

Peters, A.; Döring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349: 1582-1587.

Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997b) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.

Peters, A.; Dockery, D. W.; Heinrich, J.; Wichmann, H. E. (1997c) Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur. Respir. J. 10: 872-879.

Peters, J. M.; Avol, E.; Gauderman, W. J.; Linn, W. S.; Navidi, W.; London, S. J.; Margolis, H.; Rappaport, E.; Vora, H.; Gong, H., Jr.; Thomas, D. C. (1999a) A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am. J. Respir. Crit. Care Med. 159: 768-775.

Peters, J. M.; Avol, E.; Navidi, W.; London, S. J.; Gauderman, W. J.; Lurmann, F.; Linn, W. S.; Margolis, H.; Rappaport, E.; Gong, H., Jr.; Thomas, D. C. (1999b) A study of twelve southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am. J. Respir. Crit. Care Med. 159: 760-767.

Peters, A.; Liu, E.; Verrier, R. L.; Schwartz, J.; Gold, D. R.; Mittleman, M.; Baliff, J.; Oh, J. A.; Allen, G.; Monahan, K.; Dockery, D. W. (2000) Air pollution and incidence of cardiac arrhythmia. Epidemiology 11: 11-17.

Pinto, J. P.; Pleasant, M.; Kellogg, R.; Torok, Sz.; Stiles, D.; Willis, R. D.; Koutrakis, P.; Allen, G. A. (1995) Chemical characterization of the ambient aerosol in Philadelphia. Presented at: Particulate matter: health and regulatory issues: an A&WMA international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; submitted abstract.

Pinto, J. P.; Lefohn, A. S.; Shadwick, D. S. (2002) Aspects of the spatial variability of $PM_{2.5}$ concentrations within urban areas of the United States. Environ. Sci. Technol.: submitted.

Plopper, C. G.; Fanucchi, M. V. (2000) Do urban environmental pollutants exacerbate childhood lung diseases? Environ. Health Perspect. 108: A252-A253.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Pope, C. A.; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas, G. M.; Gold, D. R.; Dockery, D. W. (1999a) Heart rate variability associated with particulate air pollution. Am. Heart J. 138: 890-899.

Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999b) Particulate air pollution and daily mortality on Utah's Wasatch Front. Environ. Health Perspect.: 107: 567-573.

Pope, C. A., III; Eatough, D. J.; Gold, D. R.; Pang, Y.; Nielsen, K. R.; Nath, P.; Verrier, R. L.; Kanner, R. E. (2001) Acute exposure to environmental tobacco smoke and heart rate variability. Environ. Health Perspect. 109: 711-716.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect. 104: 506-514.

Ramadan, Z.; Song, X.-H.; Hopke, P. K. (2000) Identification of sources of Phoenix aerosol by positive matrix factorization. J. Air Waste Manage. Assoc. 50: 1308-1320.

Ritz, B.; Yu, F.; Fruin, S.; Chapa, G.; Shaw, G. M.; Harris, J. A. (2002) Ambient air pollution and risk of birth defects in southern California. Am. J. Epidemiol. 155: 17-25.

Romieu, I.; Meneses, F.; Ruiz, S.; Sienra, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am. J. Respir. Crit. Care Med. 154: 300-307.

Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch. Environ. Health 52: 368-376.

Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000a) National morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000b) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Hatch, G. E.; Horstman, D.; Steck-Scott, S.; Arab, L.; Bromberg, P. A.; Levine, M.; McDonnell, W. F.; Devlin, R. B. (2001) Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. Am. J. Respir. Crit. Care Med. 164: 819-825.

Sarnat, J. A.; Koutrakis, P.; Suh, H. H. (2000) Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J. Air Waste Manage. Assoc. 50: 1184-1198.

Sarnat, J. A.; Schwartz, J.; Catalano, P. J.; Suh, H. H. (2001) Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ. Health Perspect. 109: 1053-1061.

Schlesinger, R. B.; Ben-Jebria, A.; Dahl, A. R.; Snipes, M. B.; Ultman, J. (1997) Disposition of inhaled toxicants. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press; pp. 493-550.

Schwartz, J. (1997) Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377.

Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.

Schwartz, J. (2000) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151: 440-448.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology. 11: 6-10.

Schwartz, J.; Zanobetti, A. (2000) Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 11: 666-672.

Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.

Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc. 46: 927-939.

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.

Sexton, K.; Selevan, S. G.; Wagener, D. K.; Lybarger, J. A. (1992) Estimating human exposures to environmental pollutants: availability and utility of existing databases. Arch. Environ. Health 47: 398-407.

Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.

Smiley-Jewell, S. M.; Liu, F. J.; Weir, A. J.; Plopper, C. G. (2000) Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicol. Pathol. 28: 267-276.

Smith, R. L.; Spitzner, D.; Kim, Y.; Fuentes, M. (2000) Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. J. Air Waste Manage. Assoc. 50: 1367-1379.

Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol. 10: 461-477.

Thurston, G. D.; Ito, K.; Kinney, P. L.; Lippmann, M. (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. J. Exposure Anal. Environ. Epidemiol. 2: 429-450.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur. Respir. J. 13: 266-273.

Tolbert, P. E.; Klein, M.; Metzger, K. B.; Peel, J.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2000) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

Turpin, B. J. (1999) Options for characterizing organic particulate matter. Environ. Sci. Technol. 33: 76A-79A.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and PB95-124517.

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

U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants. Research Triangle Park, NC: Office of Research and Development; report nos. EPA/600/AP-93/004aF-cF. 3v. Available from: NTIS, Springfield, VA; PB96-185582, PB96-185590, and PB96-185608. Available online at: www.epa.gov/ncea/ozone.htm.

U.S. Environmental Protection Agency. (2000a) Air quality criteria for carbon monoxide. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available: www.epa.gov/ncea/co/ [2000, October 6].

U.S. Environmental Protection Agency. (2000b) Health assessment document for diesel exhaust [SAB review draft]. Washington, DC: Office of Research and Development, National Center for Environmental Assessment-Washington Office; report no. EPA/600/8-90/057E. Available: http://cfpub.epa.gov/ncea/cfm/nceahome.cfm [29 March, 2002].

U.S. Environmental Protection Agency. (2001) National air quality and emissions trends report, 1999. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA/454/R-01-004. Available: http://www.epa.gov/oar/aqtrnd99/ [11 March, 2002].

Undem, B. J.; Carr, M. J. (2002) The role of nerves in asthma. Curr. Allergy Asthma Rep. 2: 159-165.

Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am. J. Respir. Crit. Care Med. 157: 1034-1043.

Wallace, L. (2000) Correlations of personal exposure to particles with outdoor air measurements: a review of recent studies. Aerosol Sci. Technol. 32: 15-25.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol. Sci. 41: 209-216.

Watkinson, W. P.; Campen, M. J.; Nolan, J. P.; Costa, D. L. (2001) Cardiovascular and systemic responses to inhaled pollutants in rodents: effects of ozone and particulate matter. Environ. Health Perspect. 109(suppl. 4): 539-546.

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

Whitby, K. T.; Sverdrup, G. M. (1980) California aerosols: their physical and chemical characteristics. In: Hidy, G. M.; Mueller, P. K.; Grosjean, D.; Appel, B. R.; Wesolowski, J. J., eds. The character and origins of smog aerosols: a digest of results from the California Aerosol Characterization Experiment (ACHEX). New York, NY: John Wiley & Sons, Inc.; pp. 477-517. (Advances in environmental science and technology: v. 9).

Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; Research Report no. 98.

Williams, R.; Suggs, J.; Zweidinger, R.; Evans, G.; Creason, J.; Kwok, R.; Rodes, C.; Lawless, P.; Sheldon, L. (2000a) The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 1. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. J. Exposure Anal. Environ. Epidemiol. 10: 518-532.

Williams, R.; Suggs, J.; Creason, J.; Rodes, C.; Lawless, P.; Kwok, R.; Zweidinger, R.; Sheldon, L. (2000b) The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. J. Exposure Anal. Environ. Epidemiol. 10: 533-543.

Williams, R. W.; Creason, J.; Zweidinger, R.; Watts, R. R.; Shy, C. (2000c) Indoor, outdoor, and personal exposure monitoring of particulate air pollution: the Baltimore elderly epidemiology-exposure pilot study. Atmos. Environ. 34: 4193-4204.

Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.

Wilson, W. E.; Mage, D. T.; Grant, L. D. (2000) Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. J. Air Waste Manage. Assoc. 50: 1167-1183.

Wongphatarakul, V.; Friedlander, S. K.; Pinto, J. P. (1998) A comparative study of $PM_{2.5}$ ambient aerosol chemical databases. Environ. Sci. Technol. 32: 3926-3934.

Woodruff, T. J.; Grillo, J.; Schoendorf, K. C. (1997) The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. Environ. Health Perspect. 105: 608-612.

Zanobetti, A.; Schwartz, J. (2000) Race, gender, and social status as modifiers of the effects of PM_{10} on mortality. J. Occup. Environ. Med. 42: 469-474.

Zanobetti, A.; Schwartz, J. (2001) Are diabetics more susceptible to the health effects of airborne particles? Am. J. Respir. Crit. Care Med. 164: 831-833.

Zanobetti, A.; Schwartz, J.; Gold, D. (2000) Are there sensitive subgroups for the effects of airborne particles? Environ. Health Perspect. 108: 841-845.

Zanobetti, A.; Schwartz, J.; Samoli, E.; Gryparis, A.; Touloumi, G.; Atkinson, R.; Le Tertre, A.; Bobros, J.; Celko, M.; Goren, A.; Forsberg, B.; Michelozzi, P.; Rabczenko, D.; Ruiz, E. A.; Katsouyanni, K. (2002) The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. Epidemiology 13: 87-93.

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

Zhang, T.; Huang, C.; Johns, E. J. (1997) Neural regulation of kidney function by the somatosensory system in normotensive and hypertensive rats. Am. J. Physiol. 273: R1749-R1757.

Zhang, H.; Triche, E.; Leaderer, B. (2000) Model for the analysis of binary time series of respiratory symptoms. Am. J. Epidemiol. 151: 1206-1215.

Zweidinger, R.; Purdue, L.; Fitzgerald, K.; Carmichael, L.; Kellog, R. (1998) NERL PM research monitoring platforms: Baltimore, Fresno and Phoenix, data report. Research Triangle Park, NC: U.S. Environmental Protection Agency, National Exposure Research Laboratory; report no. EPA/600/R-98/138. Available from: NTIS, Springfield, VA; PB99-105660.