United States
Environmental Protection
Agency

Fourth External Review Draft of Air Quality Criteria for Particulate Matter (June, 2003):

Volume II

EPA/600/P-99/002aD
June 2003
Fourth External Review Draft

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 μm) that are capable of being deposited in thoracic (tracheobronchial and alveolar) portions of the lower respiratory tract. Later periodic reevaluation of newly available scientific information, as presented in the last previous version of this "Air Quality Criteria for Particulate Matter" document published in 1996, provided key scientific bases for PM NAAQS decisions published in July 1997. More specifically, the PM_{10} NAAQS set in 1987 (150 $\mu g/m^3$, 24-h; 50 $\mu g/m^3$, annual average) were retained in modified form and new standards (65 $\mu g/m^3$, 24-h; 15 $\mu g/m^3$, annual average) for particles $\leq$ 2.5 μm ($PM_{2.5}$) were promulgated in July 1997.

This Fourth External Review Draft of revised Air Quality Criteria for Particulate Matter assesses new scientific information that has become available mainly between early 1996

through April 2002. The present draft is being released for public comment and review by the Clean Air Scientific Advisory Committee (CASAC) to obtain comments on the organization and structure of the document, the issues addressed, the approaches employed in assessing and interpreting the newly available information on PM exposures and effects, and the key findings and conclusions arrived at as a consequence of this assessment. Public comments and CASAC review recommendations will be taken into account in making any appropriate further revisions to this document for incorporation into a final draft. Evaluations contained in the present document will be drawn on to provide inputs to associated PM Staff Paper analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose alternatives for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision of the current PM NAAQS.

Preparation of this document was coordinated by staff of EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from other EPA/ORD laboratories and academia, contributed to writing of document chapters; and earlier drafts of this document were reviewed by experts from federal and state government agencies, academia, industry, and non-governmental organizations (NGOs) for use by EPA in support of decision making on potential public health and environmental risks of ambient PM. The document describes the nature, sources, distribution, measurement, and concentrations of PM in outdoor (ambient) and indoor environments. It also evaluates the latest data on human exposures to ambient PM and consequent health effects in exposed human populations (to support decision making regarding primary, health-related PM NAAQS). The document also evaluates ambient PM environmental effects on vegetation and ecosystems, visibility, and man-made materials, as well as atmospheric PM effects on climate change processes associated with alterations in atmospheric transmission of solar radiation or its reflectance from the Earth's surface or atmosphere (to support decision making on secondary PM NAAQS).

The NCEA of EPA acknowledges the contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

Air Quality Criteria for Particulate Matter

VOLUME I

EXECUTIVE SUMMARY E-1

1. INTRODUCTION 1-1

2. PHYSICS, CHEMISTRY, AND MEASUREMENT OF PARTICULATE MATTER 2-1
   - APPENDIX 2A: Techniques for Measurement of Semivolatile Organic Compounds 2A-1
   - APPENDIX 2B: Analytical Techniques 2B-1

3. CONCENTRATIONS, SOURCES, AND EMISSIONS OF ATMOSPHERIC PARTICULATE MATTER 3-1
   - APPENDIX 3A: Spatial and Temporal Variability of the Nationwide AIRS $PM_{2.5}$ and $PM_{10-2.5}$ Data Sets 3A-1
   - APPENDIX 3B: Aerosol Composition Data from the Speciation Network 3B-1
   - APPENDIX 3C: Organic Composition of Particulate Matter 3C-1
   - APPENDIX 3D: Composition of Particulate Matter Source Emissions 3D-1
   - APPENDIX 3E: Variability Observed in $PM_{2.5}$ and $PM_{10-2.5}$ Concentrations at IMPROVE Sites 3E-1

4. ENVIRONMENTAL EFFECTS OF AIRBORNE PARTICULATE MATTER 4-1
   - APPENDIX 4A: Colloquial and Latin Names 4A-1

5. HUMAN EXPOSURE TO PARTICULATE MATTER AND ITS CONSTITUENTS 5-1

Air Quality Criteria for Particulate Matter

VOLUME II

6. DOSIMETRY OF PARTICULATE MATTER 6-1

7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS 7-1

8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER 8-1
   APPENDIX 8A: Short-Term PM Exposure-Mortality Studies: Summary Tables 8A-1
   APPENDIX 8B: Particulate Matter-Morbidity Studies: Summary Tables 8B-1

9. INTEGRATIVE SYNTHESIS 9-1
   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 9A-1

Table of Contents

Page

List of Tables . . . . . I-xvi
List of Figures . . . . . I-xxiii
Authors, Contributors, and Reviewers . . . . . I-xxix
U.S. Environmental Protection Agency Project Team for Development of Air Quality Criteria for Particulate Matter . . . . . I-xxxvii
Abbreviations and Acronyms . . . . . I-xl

6. DOSIMETRY OF PARTICULATE MATTER 6-1
6.1 INTRODUCTION 6-1
6.1.1 Size Characterization of Inhaled Particles 6-3
6.1.2 Structure of the Respiratory Tract 6-3
6.2 PARTICLE DEPOSITION 6-5
6.2.1 Mechanisms of Deposition 6-5
6.2.2 Deposition Patterns in the Human Respiratory Tract 6-7
6.2.2.1 Total Respiratory Tract Deposition 6-8
6.2.2.2 Deposition in the Extrathoracic Region 6-12
6.2.2.3 Deposition in the Tracheobronchial and Alveolar Regions 6-15
6.2.2.4 Local Distribution of Deposition 6-19
6.2.2.5 Deposition of Specific Size Modes of Ambient Aerosol 6-23
6.2.3 Biological Factors Modulating Deposition 6-24
6.2.3.1 Gender 6-25
6.2.3.2 Age 6-27
6.2.3.3 Respiratory Tract Disease 6-31
6.2.3.4 Anatomical Variability 6-34
6.2.4 Interspecies Patterns of Deposition 6-36
6.3 PARTICLE CLEARANCE AND TRANSLOCATION 6-43
6.3.1 Mechanisms and Pathways of Clearance 6-43
6.3.1.1 Extrathoracic Region 6-43
6.3.1.2 Tracheobronchial Region 6-45
6.3.1.3 Alveolar Region 6-46
6.3.2 Clearance Kinetics 6-47
6.3.2.1 Extrathoracic Region 6-48
6.3.2.2 Tracheobronchial Region 6-48
6.3.2.3 Alveolar Region 6-50
6.3.3 Interspecies Patterns of Clearance 6-54
6.3.4 Factors Modulating Clearance 6-56
6.3.4.1 Age 6-56
6.3.4.2 Gender 6-56
6.3.4.3 Physical Activity 6-56
6.3.4.4 Respiratory Tract Disease 6-56
6.4 PARTICLE OVERLOAD 6-58

Table of Contents
(cont'd)

Page

6.5 COMPARISON OF DEPOSITION AND CLEARANCE PATTERNS OF PARTICLES ADMINISTERED BY INHALATION AND INTRATRACHEAL INSTILLATION 6-60
6.6 MODELING THE DISPOSITION OF PARTICLES IN THE RESPIRATORY TRACT 6-66
6.6.1 Modeling Deposition, Clearance, and Retention 6-66
6.6.2 Models To Estimate Retained Dose 6-73
6.6.3 Fluid Dynamics Models for Deposition Calculations 6-76
6.6.4 Modeling Results Obtained with Models Available to the Public 6-82
6.6.4.1 International Commission on Radiological Protection 6-82
6.6.4.2 Multiple Path Particle Dosimetry Model 6-88
6.6.4.3 Comparisons of Deposition in Humans and Rats 6-96
6.7 SUMMARY AND CONCLUSIONS 6-102
6.7.1 Particle Dosimetry 6-102
6.7.2 Host Factors 6-102
6.7.3 Laboratory Animal Studies 6-104
6.7.4 Mathematical Models 6-104
REFERENCES 6-107

7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS 7-1
7.1 INTRODUCTION 7-1
7.2 RESPIRATORY EFFECTS OF PARTICULATE MATTER IN HEALTHY HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES 7-3
7.2.1 Ambient Combustion-Related and Surrogate Particulate Matter 7-5
7.2.1.1 Ambient Particulate Matter 7-16
7.2.1.2 Diesel Particulate Matter 7-21
7.2.1.3 Complex Combustion-Related Particles 7-27
7.2.2 Acid Aerosols 7-31
7.2.3 Metal Particles, Fumes, and Smoke 7-33
7.2.4 Ambient Bioaerosols 7-37
7.3 CARDIOVASCULAR AND SYSTEMIC EFFECTS OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES 7-39
7.4 PARTICULATE MATTER TOXICITY AND PATHOPHYSIOLOGY: IN VITRO EXPOSURES 7-53
7.4.1 Introduction 7-53
7.4.2 Experimental Exposure Data 7-53
7.4.2.1 Ambient Particles 7-62

Table of Contents
(cont'd)

Page

7.4.2.2 Comparison of Ambient and Combustion-Related Surrogate Particles 7-66
7.4.2.3 Mutagenicity 7-69
7.4.3 Potential Cellular and Molecular Mechanisms 7-69
7.4.3.1 Reactive Oxygen Species 7-69
7.4.3.2 Intracellular Signaling Mechanisms 7-76
7.4.3.3 Other Potential Cellular and Molecular Mechanisms . . . 7-80
7.4.4 Specific Particle Size and Surface Area Effects 7-82
7.5 SUSCEPTIBILITY TO THE EFFECTS OF PARTICULATE MATTER EXPOSURE 7-87
7.5.1 Pulmonary Effects of Particulate Matter in Compromised Hosts . . . 7-87
7.5.2 Genetic Susceptibility to Inhaled Particles and their Constituents . . 7-93
7.5.3 Particulate Matter Effects on Allergic Hosts 7-96
7.5.4 Resistance to Infectious Disease 7-102
7.6 RESPONSES TO PARTICULATE MATTER AND GASEOUS POLLUTANT MIXTURES 7-103
7.7 SUMMARY OF KEY FINDINGS AND CONCLUSIONS 7-114
7.7.1 Links Between Specific Particulate Matter Components and Health Effects 7-115
7.7.1.2 Acid Aerosols 7-115
7.7.1.3 Metals 7-116
7.7.1.4 Diesel Exhaust Particles 7-117
7.7.1.5 Organic Compounds 7-117
7.7.1.6 Ultrafine Particles 7-117
7.7.1.7 Concentrated Ambient Particle Studies 7-118
7.7.1.8 Bioaerosols 7-119
7.7.2 Mechanisms of Action 7-119
7.7.2.1 Direct Pulmonary Effects 7-120
7.7.2.2 Systemic Effects Secondary to Lung Injury 7-123
7.7.2.3 Direct Effects on the Heart 7-125
7.7.3 Susceptibility 7-127
7.7.4 PM Interactions with Gaseous Co-Pollutants 7-127
REFERENCES 7-129

8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER 8-1
8.1 INTRODUCTION 8-1
8.1.1 Approaches for Identifying and Assessing Studies 8-2
8.1.2 Types of Epidemiologic Studies Reviewed 8-5
8.1.3 Confounding and Effect Modification 8-8
8.1.4 GAM Convergence Issue 8-16
8.1.5 Ambient PM Increments Used to Report Risk Estimates 8-17

Table of Contents
(cont'd)

Page

8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE 8-18
8.2.1 Introduction 8-18
8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure 8-19
8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues 8-19
8.2.2.2 Newly Available Information on Short-Term Mortality Effects 8-23
8.2.2.3 New Multi-City Studies 8-30
8.2.2.4 The Role of Particulate Matter Components 8-50
8.2.2.5 New Assessments of Cause-Specific Mortality 8-70
8.2.2.6 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality 8-75
8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter 8-78
8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document 8-78
8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures 8-82
8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition 8-106
8.2.3.4 Population-Based Mortality Studies in Children 8-112
8.2.3.5 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects 8-115
8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE 8-118
8.3.1 Cardiovascular Effects Associated with Acute Ambient Particulate Matter Exposure 8-118
8.3.1.1 Introduction 8-118
8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air Quality Criteria Document 8-119
8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies 8-120
8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies 8-146
8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory-Related Hospital Admissions and Medical Visits 8-147
8.3.2.1 Introduction 8-147

Table of Contents
(cont'd)

Page

8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document 8-148
8.3.2.3 New Respiratory-Related Hospital Admissions Studies 8-149
8.3.2.4 Key New Respiratory Medical Visits Studies 8-163
8.3.2.5 Identification of Potential Susceptible Subpopulations 8-165
8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits 8-167
8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms 8-168
8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms 8-169
8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms 8-185
8.4 DISCUSSION OF EPIDEMIOLOGIC STUDIES OF HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER 8-189
8.4.1 Introduction 8-189
8.4.2 GAM Issue and Reanalyses Studies 8-192
8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Mortality 8-193
8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Respiratory Hospital Admissions 8-197
8.4.2.3 HEI Commentaries 8-201
8.4.3 Assessment of Confounding by Co-Pollutants 8-204
8.4.3.1 Introduction 8-204
8.4.3.2 Conceptual Issues in Assessing Confounding 8-206
8.4.3.3 Statistical Issues in the Use of Multi-Pollutant Models 8-207
8.4.3.4 Epidemiologic Studies of Ambient Air Pollution Interventions 8-213
8.4.4 Role of Particulate Matter Components 8-219
8.4.4.1 Fine- and Coarse-Particle Effects on Mortality 8-219
8.4.4.2 PM_{10}, $PM_{2.5}$ (Fine), and $PM_{10-2.5}$ (Coarse) Particulate Matter Effects on Morbidity 8-229
8.4.5 The Question of Lags 8-234
8.4.6 Concentration-Response Relationships for Ambient PM 8-238
8.4.7 Heterogeneity of Particulate Matter Effects Estimates 8-241

Table of Contents
(cont'd)

Page

8.4.7.1 Evaluation of Heterogeneity of Particulate Matter Mortality Effect Estimates 8-243
8.4.7.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies 8-247
8.4.8 New Assessments of Measurement Error Consequences 8-248
8.4.8.1 Theoretical Framework for Assessment of Measurement Error 8-248
8.4.8.2 Spatial Measurement Error Issues That May Affect the Interpretation of Multi-Pollutant Models with Gaseous Co-Pollutants 8-255
8.4.8.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in Multi-Pollutant Models. 8-263
8.4.8.4 Air Pollution Exposure Proxies in Long-Term Mortality Studies 8-264
8.4.9 Implications of Airborne Particle Mortality Effects 8-268
8.4.9.1 Short-Term Exposure and Mortality Displacement 8-268
8.4.9.2 Life-Shortening Estimates Based on Semi-Individual Cohort Study Results 8-273
8.4.9.3 Potential Effects of Infant Mortality on Life-Shortening Estimates 8-274
8.5 SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES 8-274
REFERENCES 8-282

APPENDIX 8A: Short-Term PM Exposure-Mortality Studies: Summary Table 8A-1

APPENDIX 8B: Particulate Matter-morbidity Studies: Summary Tables 8B-1
Appendix 8B.1: PM-Cardiovascular Admissions Studies 8B-2
Appendix 8B.2. PM-Respiratory Hospitalization Studies 8B-19
Appendix 8B.3: PM-Respiratory Visits Studies 8B-42
Appendix 8B.4: Pulmonary Function Studies 8B-53
Appendix 8B.5: Short-Term PM Exposure Effects On Symptoms in Asthmatic Individuals 8B-59
Appendix 8B.6: Short-Term PM Exposure Effects on Pulmonary Function in Nonasthmatics 8B-65
Appendix 8B.7: Short-Term PM Exposure Effects on Symptoms in Nonasthmatics 8B-73
Appendix 8B.8: Long-Term PM Exposure Effects on Respiratory Health Indicators, Symptoms, and Lung Function 8B-78

9. INTEGRATIVE SYNTHESIS 9-1

Table of Contents
(cont'd)

Page

9.1 INTRODUCTION 9-1
9.1.1 Legislative Requirements and Past NAAQS Reviews 9-1
9.1.2 Organization of the Chapter 9-4
9.2 BACKGROUND 9-6
9.2.1 Basic Concepts 9-6
9.2.2 Particle Size Distributions 9-6
9.2.3 Definitions of Particle Size Fractions 9-7
9.3 CHARACTERIZATION OF PM SOURCES 9-15
9.4 AMBIENT CONCENTRATIONS 9-19
9.4.1 Measurement of Particulate Matter 9-19
9.4.2 Mass Concentrations 9-21
9.4.3 Physical and Chemical Properties of Ambient PM 9-21
9.5 EXPOSURE TO PARTICULATE MATTER AND CO-POLLUTANTS 9-25
9.5.1 Central Site to Outdoor Relationships 9-25
9.5.1.1 Exposure for Acute Epidemiology 9-25
9.5.1.2 Exposure for Chronic Epidemiology 9-26
9.5.2 Home Outdoor Concentrations Versus Concentrations of Ambient PM Infiltrated Indoors 9-28
9.5.2.1 Mass Balance Model 9-28
9.5.2.2 Separation of Total Personal Exposure into its Ambient and Nonambient Components 9-29
9.5.3 Variability in the Relationship Between Outdoor Concentrations and Personal Exposures 9-32
9.5.4 Exposure Relations for Co-Pollutants 9-33
9.5.5 Exposure Relationships for Susceptible Subpopulations 9-38
9.5.6 Air Pollutants Generated Indoors 9-38
9.6 DOSIMETRY: DEPOSITION AND FATE OF PARTICLES IN THE RESPIRATORY TRACT 9-39
9.6.1 Particle Deposition in the Respiratory Tract 9-39
9.6.2 Particle Clearance and Translocation 9-45
9.6.3 Dosimetric Considerations in Comparing Dosages for Inhalation, Instillation, and Exposure of Cultured Cells 9-47
9.6.4 Inhaled Particles as Potential Carriers of Toxic Agents 9-49
9.7 TOXICOLOGIC ASSESSMENT OF PARTICULATE-MATTER PROPERTIES LINKED TO HEALTH EFFECTS 9-50
9.7.1 Chemical Components and Source Categories Associated with Health Effects in Epidemiologic Studies 9-52
9.7.1.1 Toxicologically Important Components of PM 9-52
9.7.1.2 Source Category Factors 9-53
9.7.2 Specific Properties of Ambient PM Linked to Health Effects 9-55
9.7.2.1 Physical Properties 9-55
9.7.2.2 Chemical Properties 9-57

Table of Contents
(cont'd)

Page

9.7.2.3 Summary 9-61
9.7.3 Mechanisms of Action Underlying PM Cardiovascular Effects 9-61
9.8 HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER OBSERVED IN HUMAN POPULATION STUDIES 9-66
9.8.1 Introduction 9-66
9.8.1.2 GAM Convergence Issue 9-70
9.8.1.3 Ambient PM Increments Used to Report Risk Estimates 9-71
9.8.2 Short-Term Particulate Matter Exposure Effects on Mortality 9-72
9.8.2.1 Methodological Issues for Short-Term Exposure Studies 9-111
9.8.3 Health Effects of Long-Term Exposures to Particulate Matter 9-118
9.8.4 Coherence of Reported Epidemiologic Findings 9-127
9.9 SUSCEPTIBLE SUBPOPULATIONS AND IMPLICATIONS OF EFFECTS OF AMBIENT PM EXPOSURE ON HUMAN HEALTH 9-129
9.9.1 Introduction 9-129
9.9.2 Preexisting Disease as a Risk Factor for Particulate Matter Health Effects 9-130
9.9.2.1 Ambient PM Exacerbation of Cardiovascular Disease Conditions 9-130
9.9.2.2 Ambient PM Exacerbation of Respiratory Disease Conditions 9-133
9.9.3 Age-Related At-Risk Population Groups: The Elderly and Children 9-135
9.9.4 Impact on Life-Expectancy 9-138
9.10 INTEGRATIVE SYNTHESIS OF KEY FINDINGS FOR ENVIRONMENTAL EFFECTS OF AMBIENT AIRBORNE PM 9-139
9.10.1 Introduction 9-139
9.10.2 Effects of Ambient Airborne PM on Vegetation and Natural Ecosystems 9-139
9.10.2.1 Ecological Attributes 9-141
9.10.2.2 Ecosystem Exposures – Particle Deposition 9-143
9.10.2.3 Direct and Indirect Effects on Ecosystems 9-143
9.10.3 Visibility Effects of Airborne Particles 9-149
9.10.4 Materials Damage Related to Airborne Particulate Matter 9-151
9.10.5 Atmospheric Particle Effects on Global Warming Processes and Transmission of Solar Ultraviolet Radiation 9-152
REFERENCES 9-154

Table of Contents
(cont'd)

Page

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 9A-1
REFERENCES 9A-6

List of Tables

Number		Page
6-1	Effects of Age on Particle Deposition in Respiratory Tract	6-28
6-2	Overview of Respiratory Tract Particle Clearance and Translocation Mechanisms	6-44
6-3	Respiratory Parameters Used in LUDEP Model	6-84
6-4	Levels of Physical Exertion for Adult, Corresponding Representative Activities, and Breathing Parameters	6-90
6-5	Parameters Used in Age Dependent Calculations of the CIIT/RIVM Deposition Model	6-92
6-6	Respiratory Parameters for Humans and Rats	6-97
6-7	Surface Areas of Tracheobronchial and Alveolar Regions for Humans and Rats	6-100
7-1a	Respiratory Effects of Inhaled Ambient Particulate Matter in Controlled Exposure Studies of Human Subjects and Laboratory Animals	7-6
7-1b	Respiratory Effects of Instilled Ambient Particulate Matter in Laboratory Animals and Human Subjects	7-7
7-2a	Respiratory Effects of Instilled Complex Combustion-related Particulate Matter in Laboratory Animals	7-8
7-2b	Respiratory Effects of Inhaled Complex Combustion-related Particulate Matter in Compromised Laboratory Animal Models	7-12
7-3	Respiratory Effects of Surrogate Particulate Matter in Laboratory Animals	7-13
7-4	Respiratory Effects of Acid Aerosols in Humans and Laboratory Animals	7-32
7-5a	Respiratory Effects of Instilled Metal Particles, Fumes, and Smoke in Human Subjects and Laboratory Animals	7-34
7-5b	Respiratory Effects of Inhaled Metal Particles, Fumes, and Smoke in Humans and Laboratory Animals	7-35
7-6	Controlled Exposure Studies of Respiratory Effects of Inhaled Ambient Bioaerosols	7-38

List of Tables
(cont'd)

Number		Page
7-7a	Cardiovascular and Systemic Effects of Instilled Ambient and Combustion-Related Particulate Matter	7-40
7-7b	Cardiovascular and Systemic Effects of Inhaled Ambient and Combustion-Related Particulate Matter	7-42
7-8	Physicochemical Properties of Particulate Matter	7-54
7-9	In Vitro Effects of Particulate Matter and Particulate Matter Constituents	7-55
7-10	Mutagenic/Carcinogenic Effects of Particulate Matter	7-70
7-11	Numbers and Surface Areas of Monodisperse Particles of Unit Density of Different Sizes at a Mass Concentration of 10 $\mu g/m^3$	7-83
7-12	Respiratory and Cardiovascular Effects of PM and Gaseous Pollutant Mixtures	7-105
8-1	Recent U.S. and Canadian Time-Series Studies of PM-Related Daily Mortality	8-24
8-2	Synopsis of Short-Term Mortality Studies that Examined Relative Importance of $PM_{2.5}$ and $PM_{10-2.5}$	8-52
8-3	Newly Available Studies of Mortality Relationships to PM Chemical Components	8-62
8-4	Summary of Source-Oriented Evaluations of PM Components in Recent Studies	8-67
8-5	Comparison of Six Cities and American Cancer Society Study Findings from Original Investigators and Health Effects Institute Reanalysis	8-84
8-6	Relative Risk of All-Cause Mortality for Selected indices of Exposure to Fine Particulate Matter (per 18.6 $\mu g/m^3$) Based on Multivariate Poisson Regression Analysis, by Age Group, for Harvard Six City Study Data	8-88
8-7	Summary of Results from the Extended ACS Study	8-90
8-8	Relative Risk of Mortality from All Nonexternal Causes, by Sex and Air Pollutant, for an Alternative Covariate Model in the ASHMOG Study	8-97

List of Tables
(cont'd)

Number		Page
8-9	Relative Risk of Mortality from Cardiopulmonary Causes, by Sex and Air Pollutant, for an Alternative Covariate Model in the ASHMOG Study	8-98
8-10	Relative Risk of Mortality from Lung Cancer by Air Pollutant and by Gender for an Alternative Covariate Model	8-99
8-11	Comparison of Excess Relative Risks of Long-Term Mortality in the Harvard Six Cities, ACS, AHSMOG, and VA Studies	8-104
8-12	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	8-107
8-13	Comparison of Reported $SO_4^=$ and $PM_{2.5}$ Relative Risks for Various Mortality Causes in the American Cancer Society Study	8-108
8-14	Comparison of Total Mortality Relative Risk Estimates and T-Statistics for Particulate Matter Components in Three Prospective Cohort Studies	8-109
8-15	Comparison of Cardiopulmonary Mortality Relative Risk Estimates and T-Statistics for Particulate Matter Components in Three Prospective Cohort Studies	8-110
8-16	Summary of Studies of PM_{10}, $PM_{10-2.5}$, or $PM_{2.5}$ Effects on Total CVD Hospital Admissions and Emergency Visits	8-121
8-17	Summary of United States PM_{10} Respiratory-Related Hospital Admission Studies	8-150
8-18	Percent Increase in Hospital Admissions per 10-$\mu g/m^3$ Increase in PM_{10} in 14 U.S. Cities (original and reanalyzed results)	8-152
8-19	Summary of United States $PM_{2.5}$ Respiratory-Related Hospital Admission Studies	8-156
8-20	Summary of United States $PM_{10-2.5}$ Respiratory-Related Hospital Admission Studies	8-157
8-21	Intercomparison of Detroit Pneumonia Hospital Admission Relative Risks (± 95% CI below) of PM Indices (per 5^{th}-to-95^{th} percentile pollutant Increment) for Various Model Specifications	8-158

List of Tables
(cont'd)

Number		Page
8-22	Summary of United States PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ Asthma Medical Visit Studies	8-163
8-23	Summary of Quantitative PFT Changes in Asthmatics per 50 $\mu g/m^3$ PM_{10} Increment	8-171
8-24	Summary of PFT Changes in Asthmatics per 25 $\mu g/m^3$ $PM_{2.5}$ Increment	8-172
8-25	Summary of Asthma PM_{10} Cough Studies	8-175
8-26	Summary of Asthma PM_{10} Phlegm Studies	8-176
8-27	Summary of Asthma PM_{10} Lower Respiratory Illness Studies	8-176
8-28	Summary of Asthma PM_{10} Bronchodilator Use Studies	8-177
8-29	Summary of Asthma $PM_{2.5}$ Respiratory Symptom Studies	8-179
8-30	Summary of Non-Asthma PM_{10} PFT Studies	8-181
8-31	Summary of Non-Asthma PM_{10} Respiratory Symptom Studies	8-182
8-32	Summary of Non-Asthma $PM_{2.5}$ Respiratory Outcome Studies	8-183
8-33	Summary of Non-Asthma Coarse Fraction Studies of Respiratory Endpoints	8-184
8-34	PM_{10} Excess Risk Estimates from Reanalysis Studies for Total Non-Accidental Mortality per 50 $\mu g/m^3$ Increase in PM_{10}	8-194
8-35	Comparison of Maximum Single Day Lag Effect Estimates for $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} for Seattle Asthma Hospital Admissions Based on Original Gam Analyses Using Default Convergence Criteria Versus Reanalyses Using GAM with More Stringent Convergence Criteria and GLM	8-199
8-36	Comparison of Los Angeles COPD Hospital Admissions Maximum Single Day Lag Effect Estimates for $PM_{2.5}$ and PM_{10} from the Original GAM Analyses Using Default Convergence Criteria Versus for Reanalyses Using More Stringent Convergence Criteria and for Models Smoothed with More Degrees of Freedom	8-201

List of Tables
(cont'd)

Number		Page
8-37	Summary of Past Ecologic and Case-Control Epidemiologic Studies of Outdoor Air and Lung Cancer	8-225
8-38	Maximum, Mean, 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	8-259
8-39	Summary of Within-City Heterogeneity by Region	8-260
8-40	Summary of ACS Pollution Indices: Units, Primary Sources, Number of Cities and Subjects Available for Analysis, and the Mean Levels (standard deviations)	8-269
8A-1	Short-Term Particulate Matter Exposure Mortality Effects Studies	8A-2
8B-1	Acute Particulate Matter Exposure and Cardiovascular Hospital Admissions	8B-3
8B-2	Acute Particulate Matter Exposure and Respiratory Hospital Admissions Studies	8B-20
8B-3	Acute Particulate Matter Exposure and Respiratory Medical Visits	8B-43
8B-4	Short-Term Particulate Matter Exposure Effects on Pulmonary Function Tests in Studies of Asthmatics	8B-54
8B-5	Short-term Particulate Matter Exposure Effects on Symptoms in Studies of Asthmatics	8B-60
8B-6	Short-Term Particulate Matter Exposure Effects on Pulmonary Function Tests in Studies of Nonasthmatics	8B-66
8B-7	Short-Term Particulate Matter Exposure Effects on Symptoms in Studies of Nonasthmatics	8B-74
8B-8	Long-Term Particulate Matter Exposure Respiratory Health Indicators: Respiratory Symptom, Lung Function	8B-79
9-1	Constituents of Atmospheric Particles and Their Major Sources	9-16

List of Tables
(cont'd)

Number		Page
9-2	Comparison of Ambient Particles, Fine (ultrafine plus accumulation mode) and Coarse	9-22
9-3	Concentrations of $PM_{2.5}$, $PM_{10-2.5,}$ and Selected Elements in the $PM_{2.5}$ and $PM_{10-2.5}$ Size Range	9-23
9-4	Qualitative Estimates of Exposure Variables	9-36
9-5	Concentration Differences Between Constituents of Nonambient (indoor-generated) and Ambient PM	9-39
9-6	Particulate Matter Associated with Mortality in Epidemiologic Studies	9-52
9-7	Source Categories Associated with Mortality in Epidemiologic Studies	9-54
9-8	Estimated Total, Cardiovascular and Respiratory Mortality Effect Sizes per Increments in 24-h Concentrations of PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ from U.S. and Canadian Studies	9-77
9-9	Summary of Source-oriented Evaluations of PM Components in Recent Studies	9-89
9-10	Cardiovascular and Respiratory-Related Morbidity Effect Size Estimates per Increment in 24-h Concentrations of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in U.S. and Canadian Studies	9-91
9-11	Effect Estimates per Increments in Long-Term Mean Levels of Fine and Coarse Fraction Particle Indicators from U.S. and Canadian Studies	9-119
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)	9-131
9-13	Number of Acute Respiratory Conditions per 100 Persons per Year, by Age: United States, 1996	9-136
9-14	Essential Ecological Attributes and Reporting Categories	9-142
9-15	Effects of Reactive Nitrogen	9-148
9A-1	Effect Estimates per 50-$\mu g/m^3$ Increase in 24-Hour PM_{10} Concentrations From U.S. and Canadian Studies	9A-2

List of Tables
(cont'd)

Number		Page
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	9A-4
9A-3	Effect Estimates per Increments in Annual Mean Levels of Fine Particle Indicators from U.S. and Canadian Studies	9A-5

List of Figures

Number		Page
6-1	Diagrammatic representation of respiratory tract regions in humans	6-4
6-2	Total respiratory tract deposition (as percentage deposition of amount inhaled) in humans as a function of particle size	6-9
6-3	Total deposition fraction as a function of particle size in 22 healthy men and women under six different breathing patterns	6-11
6-4	Extrathoracic deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size	6-13
6-5	Tracheobronchial deposition (oral inhalation as percentage deposition of the amount inhaled) in humans as a function of particle size	6-16
6-6	Alveolar deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size	6-16
6-7	Lung deposition fractions in the tracheobronchial (TB) and alveolar (A) regions estimated by the bolus technique	6-18
6-8	Estimated lung deposition fractions in ten volumetric regions for particle sizes ranging from ultrafine particle diameter (d_p) of 0.04 to 0.01 μm (Panel A) to fine (d_p = 1.0 μm; Panel B) and coarse (d_p = 3 and 5 μm; Panels C and D)	6-22
6-9	Regional deposition fraction measured in laboratory animals as a function of particle size for (a) upper respiratory tract, (b) tracheobronchial region, and (c) pulmonary region	6-38
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	6-39
6-11	Major clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree	6-44
6-12	Diagram of known and suspected clearance pathways for poorly soluble particles depositing in the alveolar region	6-45
6-13	Percent deposition for total results of LUDEP model for an adult male worker (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions	6-85

List of Figures
(cont'd)

Number		Page
6-14	Percent deposition for total results of LUDEP model for a young adult (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions	6-86
6-15	Comparison of percent deposition in the TB and A regions for a worker (WK; light exercise) and a young adult (YA; resting)	6-87
6-16	Dependency of aerosol deposition in human adults on physical exertion expressed as minute ventilation for different particle sizes	6-91
6-17	Age dependency of human aerosol deposition for different particle sizes	6-93
6-18	Age dependency of human standardized aerosol deposition for different particle sizes	6-95
6-19	Comparison of percent deposition for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat for nasal and mouth breathing humans for the ET (a), TB (b), and A (c) regions of the respiratory tract	6-97
6-20	Normalized deposition patterns for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat for nasal and mouth breathing humans for the thoracic region (in terms of μg PM per g of lung)	6-99
6-21	Normalized deposition patterns arising from 8 hr exposure to 100 $\mu g/m^3$, based on EPA default values of surface area, for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat (a) for the TB region (in units of μg PM per m^2 TB area) and (b) for the A region (in terms of μg PM per m^2 of A)	6-100
6-22	Normalized deposition patterns arising from 8 hr exposure to 100 $\mu g/m^3$, based on surface area values from Winter-Sorkina and Cassee (2002), for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat (a) for the TB region (in units of μg PM per m^2 TB area) and (b) for the A region (in terms of μg PM per m^2 of A)	6-101
8-1a	Strong within-city association between PM and mortality, but no second-stage association	8-11
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	8-11

List of Figures
(cont'd)

Number		Page
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	8-13
8-3	Estimated excess risks for PM mortality (1 day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis	8-32
8-4	Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses	8-33
8-5	Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-$\mu g/m^3$ increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 8-4	8-34
8-6	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	8-36
8-7	Percent excess risks estimated per 25 $\mu g/m^3$ increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10-2.5}$, based on single pollutant (PM only) model	8-55
8-8	Excess risks estimated per 5 $\mu g/m^3$ increase in sulfate, based on the studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available	8-65
8-9	Natural logarithm of relative risk for total and cause-specific mortality per 10 $\mu g/m^3$ $PM_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions	8-91
8-10	Relative risk of total and cause-specific mortality at 10 $\mu g/m^3$ $PM_{2.5}$ (mean of 1979-1983) of alternative statistical models	8-92
8-11	Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses)	8-93
8-12	Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from selected U.S. PM_{10} studies based on single-pollutant models	8-137
8-13	Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma	8-160

List of Figures
(cont'd)

Number		Page
8-14	Maximum excess risk of respiratory-related hospital admissions and visits per 50 $\mu g/m^3$ PM_{10} increment in selected studies of U.S. cities based on single-pollutant models	8-168
8-15	Selected acute pulmonary function change studies of asthmatic children	8-173
8-16	Odds ratios with 95% confidence interval for cough per 50-$\mu g/m^3$ increase in PM_{10} for selected asthmatic children studies at lag 0	8-178
8-17	PM_{10} excess risk estimates for total non-accidental mortality for numerous locations (and for cardiovascular mortality[*] for Coachella Valley, CA and Phoenix, AZ), using: (1) GAM with default convergence criteria (white circle); (2) GAM with stringent convergence criteria (black circle); and, (3) GLM/natural splines (x) that approximate the original GAM model from the GAM reanalysis studies	8-195
8-18	Comparison of GAM results for original (default) convergence case versus those from reanalyses with a more stringent convergence criterion (10e-15) for constrained lag respiratory model cases	8-198
8-19	Marginal posterior distribution for effects of PM_{10} on all cause mortality at lag 0, 1, and 2 for the 90 cities	8-235
8-20	Particulate matter < 10 μm in aerodynamic diameter (PM_{10})-total mortality concentration-response curves for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (OTHERS) mortality, 20 largest US cities, 1987-1994	8-239
8-21	An EPA-derived plot showing relationship of PM_{10} total mortality effects estimates and 95% confidence intervals for all cities in the Dominici et al. (2000a; 2003) NMMAPS 90-cities analyses in relation to study size (i.e., the natural logarithm or numbers of deaths times days of PM observations)	8-244
8-22	The EPA-derived plots showing Dominici et al. (2003) relationships of PM_{10}-mortality (total, nonaccidental) effects estimates and 95% confidence intervals to study size (defined as in Figure 8-10) for cities broken out by regions as per the NMMAPS regional analyses of Samet et al. (2000a,b)	8-245
8-23	Concentration of PM_{10} and NO_2 versus distance	8-258
9-1	A general framework for integrating particulate-matter research	9-6

List of Figures
(cont'd)

Number		Page
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	9-8
9-3	Volume size distribution, measured in traffic, showing fine and coarse particles and the nuclei and accumulation modes within the fine particles	9-9
9-4	Submicron number size distribution observed in a boreal forest in Finland showing the tri-modal structure of fine particles	9-10
9-5	Specified particle penetration (size-cut curves) through an ideal (no-particle-loss) inlet for five different size-selective sampling criteria	9-13
9-6	An idealized distribution of ambient particulate matter showing the accumulation mode and the coarse mode and the size fractions collected by size-selective samplers	9-14
9-7	Schematic showing major nonvolatile and semivolatile components of $PM_{2.5}$	9-20
9-8	Major chemical components of $PM_{2.5}$ as determined in the U.S. Environmental Protection Agency's national speciation network from October 2001 to September 2002	9-24
9-9	Occurrence of differences between pairs of sites in three MSAs	9-27
9-10	Regression analysis of daytime total personal exposures to PM_{10} versus ambient PM_{10} concentrations using data from the PTEAM study	9-30
9-11	Regression analysis of daytime exposures to the ambient component of personal exposure to PM_{10} (ambient exposure) versus ambient PM_{10} concentrations	9-31
9-12	Percentage of homes with air conditioning versus the regression coefficient for the relationship of cardiovascular-related hospital admissions to ambient PM_{10} concentrations	9-33
9-13	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	9-34

List of Figures
(cont'd)

Number		Page
9-14	Percent deposition for total results of LUDEP model for an adult male worker (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions	9-42
9-15	Schematic representation of potential pathophysiological pathways and mechanisms by which ambient PM may increase risk of cardiovascular morbidity and/or mortality	9-62
9-16	Percent excess risks estimated per 25-$\mu g/m^3$ 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	9-86
9-17	Relative risks estimated per 5-$\mu g/m^3$ increase in sulfate from U.S. and Canadian studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available	9-88
9-18	Acute cardiovascular hospitalizations and PM exposure excess risk estimates derived from selected U.S. PM_{10} studies	9-102
9-19	Maximum excess risk in selected studies of U.S. cities relating PM_{10} estimate of exposure (50 $\mu g/m^3$) to respiratory-related hospital admissions and visits	9-106
9-20	Selected acute pulmonary function change studies of asthmatic children	9-109
9-21	Odds ratios for cough for a 50-$\mu g/m^3$ increase in PM_{10} for selected asthmatic children studies, with lag 0 with 95% CI	9-110
9-22	Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1, with and without control for other pollutants, for the NMMAPS 90 cities	9-113
9-23	Inhalation rates on a per body-weight basis for males (■) and females (▲) by age (Layton, 1993)	9-137
9-24	Illustration of the nitrogen cascade showing the movement of the human-produced reactive nitrogen (Nr) as it cycles through the various environmental reservoirs in the atmosphere, terrestrial ecosystems, and acquatic ecosystems	9-146

Authors, Contributors, and Reviewers

CHAPTER 6. DOSIMETRY OF PARTICULATE MATTER

Principal Authors

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

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

Dr. James McGrath—Chapel Hill, NC 27517

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

Contributing Authors

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

Contributors and Reviewers

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

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

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

Dr. Kevin Dreher—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

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

Dr. John Godleski—Weston, MA 02493

Contributors and Reviewers
(cont' d)

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

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

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

Dr. Ted Martonen—National Health and Environmental Effects Research Laboratory (MD-74), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Gunter Oberdorster—University of Rochester, Department of Environmental Medicine, Rochester, NY 14642

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

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

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

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

Dr. William Watkinson—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Principal Authors

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

Authors, Contributors, and Reviewers
(cont' d)

Principal Authors
(cont'd)

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

Dr. James McGrath—Chapel Hill, NC 27517

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

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

Contributors and Reviewers

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

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

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

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

Dr. Kevin Dreher—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Janice Dye—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

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

Dr. Ian Gilmour—National Health and Environmental Effects Research Laboratory (MD-92), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers
(cont'd)

Dr. John Godleski—Weston, MA 02493

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

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

Dr. Urmila Kodavanti—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

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

Dr. Ted Martonen—National Health and Environmental Effects Research Laboratory (MD-74), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Gunter Oberdorster—University of Rochester, Department of Environmental Medicine, Rochester, NY 14642

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

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

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

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

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

Bellina Veronesi—National Health and Environmental Effects Research Laboratory (MD-74B), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers
(cont'd)

Dr. William Watkinson—National Health and Environmental Effects Research Laboratory (MD-82), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Principal Authors

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

Dr. Vic Hasselblad—Durham, NC 27713

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

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

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

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

Contributing Authors

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

Contributors and Reviewers

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

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

Contributors and Reviewers
(cont.)

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

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

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

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

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

Dr. Fred Lipfert—Northport, NY 11768

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

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

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

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

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

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

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

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

Contributors and Reviewers
(cont'd)

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

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

Principal Authors

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

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

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

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

Contributors and Reviewers

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

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

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

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

Contributors and Reviewers
(cont'd)

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

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

Executive Direction

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

Scientific Staff

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

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

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

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

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

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

Technical Support Staff

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

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

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

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

Technical Support Staff
(cont'd)

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

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

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

Document Production Staff

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

Mr. Charles E. Gaul—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Mr. John M. Havel—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

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

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

Ms. Kelly Quiñones—Word Processor, InfoPro, Inc., 8200 Greensboro Drive, Suite 1450, McLean, VA 22102

Ms. Laura A. Rhodes—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Mr. Keith A. Tarpley—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

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

Technical Reference Staff

Mr. John A. Bennett—Technical Information Specialist, SANAD Support Technologies, Inc., 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

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

Ms. Sandra L. Hughey—Technical Information Specialist, SANAD Support Technologies, Inc., 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Abbreviations and Acronyms

4-POBN	α-(4-pyridyl-1-oxide)-N-tert-butylnitrone
A	alveolar
ACE	acetone
ADS	anatomic dead space
AED	aerodynamic equivalent diameter
AHSMOG	Adventist Health Study on Smog
AIC	Akaike Information Criterion
AM	alveolar macrophage
BAD	brachial artery diameter
BAL	bronchoalveolar lavage
BALF	brochoalveolar lavage fluid
BAUS	brachial artery ultrasonography
BHR	bronchial hyperreactivity
BIC	Bayes Information Criterion
BMI	body mass index
BW	bronchial wash
CAPs	concentrated ambient particles
CAT	computer-aided tomography
CB	chronic bronchitis
CESAR	Central European Air Quality and Respiratory Health
CF	cystic fibrosis
CFA	coal fly ash
CFD	computational fluid dynamics
CHF	congestive heart failure
CIIT	Chemical Industry Institute of Technology
CL	chemiluminescence

CMD	count mean diameter
CMP	copper smelter dust
CoH	coefficient of haze
COHb	carboxyhemoglobin
CP	coarse particle
CPZ	capsazepine
CR	concentration-response
CRC	contributing respiratory causes
CrD	cerebrovascular disease
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CVD	cardiovascular disease
CVM	cardiovascular mortality
CX	cyclohexane
DBP	diastolic blood pressure
DCFH	dichlorofluorescin
DCM	dichloromethane
DE	diesel exhaust
DE	deposition efficiencies
DEF	Deferoxamine
DEP	diesel exhaust particles
DHR	dihydrorhodamine-123
DMTU	dimethylthiourea
DOFA	domestic oil fly ash
DPM	diesel particulate matter
DRG	dorsal root ganglia
DTPA	techetium-diethylenetriamine-pentaacetic acid
DYS	dysrhythmias
ECG	electrocardiogram

ED	emergency department
EGA	evolved gas analysis
EGF	epidermal growth factor
EPEC	Ecological Processes and Effects Committee
EPM	emission particulate matter
ER	excess risk
ERK	extracellular receptor kinase
ESR	electron spin resonance
ET	extrathoracic
EU	endotoxin units
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1
FMD	flow-mediated dilation
FP	fine particle
FPD	flame photometric detector
FVC	forced vital capacity
G6PDH	glucose-6-phosphate dehydrogenase
GLM	Generalized Linear Model
GMCSF	granulocyte macrophage colony stimulating factor
GMPD	geometric mean particle diameter
GP	general practice
GSF	Gessellschaft fur Strahlenforschung
GSH	glutathione
HDM	house dust mite
HF	high frequency
HR	heart rate
IκBα	inhibitory kappa B alpha
ICAM-1	intercellular adhesion molecule-1

ICD9	International Classification of Disease
ICRP	International Commission on Radiological Protection
IgE	immunoglobin E
IgG	immunoglobin G
IHD	ischemic heart disease
IL	interleukin
ip	intraperitoneal
IP	inhalable particle
IQR	interquartile range
IUGR	intrauterine growth retardation
JNK	c-jun N-terminal kinase
KS	soil-corrected potassium
LCL	lower 95^{th}% confidence limit
LDH	lactate dehydrogenase
LF	low frequency
LFA-1	leukocyte function-associated antigen-1
LN	lymph nodes
LPS	lipopolysaccharide
LRD	lower respiratory disease
LRI	lower respiratory illness
MAPK	mitogen-activated protein kinase
MAS	Mobil Aerosol Spectrometer
MC	mass concentration
MCM	mass concentrations monitor
MCT	monocrotaline
MEK	mitogen-activated protein kinase
MIP	macrophage inflammatory protein
MMAD	mean median aerodynamic diameter (see σ_g)

MMD	mass median diameter
MMPs	matrix metalloproteinases
MPL	multipath lung
MPO	myeloperoxidase
MPPD	multiple path particle dosimetry
MSH	Mount St. Helens
NAC	N-acetylcysteine (antioxidant)
NAL	nasal lavage fluid
NC	number concentration
NCRP	National Council on Radiation Protection and Measurement
NF	nuclear factor
NF-κB	nuclear factor kappa B
NHBE	normal human bronchial epithelial
NMD	nitroglycerine-mediated dilation
NMD	number mean diameter
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMRI	Naval Medical Research Institute
Nn	numerical density of neutrophils
NOPL	nasa-oro-pharyngo-laryngeal
OAA	Ottowa ambient air
OLS	ordinary least squares
OTT	Ottawa dust
OVA	ovalbumin
PB	polymyxin-B
PDGF	platelet-derived growth factor
PDL	polynomial distributed lag
PEF	peak expiratory flow
PFA	pulverized fuel ash

PFT	pulmonary function tests
PHS-2	prostaglandin H synthase-2
PMN	polymorphonuclear leukocytes
p^o	equilibrium vapor pressure
poly I:C	polyionosinic-polycytidilic acid
PTFE	polytetrafluoroethylene
PVCs	premature ventricular complexes
QHIP	Quebec Health Insurance Plan
r-MSSD	root mean squared differences between adjacent normal-to-normal heartbeat intervals
RAIV	rat-adapted influenza virus
RAPS	Regional Air Pollution Study
RCAL	Regression Calibration
RIVM	Directorate-General for Environmental Protection
ROFA	residual oil fly ash
ROS	reactive oxygen species
RR	relative risk
RSP	respirable particulate matter
RTE	rat tracheal epithelial
SAD	small airway disease
SCA	sudden cardiac arrest
SDANN	standard deviation of the average of normal-to-normal heartbeat intervals
SDMM	standard deviation of normal-to-normal heartbeat intervals
SH	spontaneously hypertensive
SHEDS	Stochastic Human Exposure and Dose Simulation
SIMEX	Simulation Extrapolation
SIXE	synchrotron induced X-ray emission
SL	stochastic lung

SOD	superoxide dismutase
SPM	synthetic polymer monomers
SpO_2	oxygen saturation
Stk	Stokes number
SWMMC	Southwest Metropolitan Mexico City
T(CO)	core temperature
TB	tracheabronchial
TDF	total deposition fraction
TIMP	tissue inhibitor of metalloproteinase
UAP	urban air particles
UCL	upper 95th% confidence limit
ufCB	ultrafine carbon black
UFP	ultrafine fluorospheres
URT	upper respiratory tract
UVD	Utah Valley dust
VA	Veterans' Administration
VBE	Japanese B encephalitis
VCAM-1	vascular cell adhesion molecule-1
VMTD	vehicle miles of travel per mi^2 per year by diesel
VMTG	vehicle miles of travel per mi^2 per year by gasoline
WEE	western equine encephalitis
WIS	Wistar
WKY	Wistar-Kyoto

6. DOSIMETRY OF PARTICULATE MATTER

6.1 INTRODUCTION

The proximal cause of any biological response to particulate matter (PM) is the dose delivered to the target site rather than the external exposure. Characterization of the exposure-dose-response continuum for PM requires an understanding of the mechanistic determinants of inhaled particle dose. Furthermore, dosimetric information is critical to extrapolating to humans health effects demonstrated by toxicological studies using experimental animals and for comparing results from controlled clinical studies involving healthy human subjects and those with preexisting respiratory disease.

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

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

The dose from inhaled particles deposited and retained in the respiratory tract is governed by a number of factors. These include exposure concentration and exposure duration, respiratory tract anatomy and ventilatory parameters, and physicochemical properties of the particles themselves (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). The basic characteristics of particles as they relate to deposition and retention, as well as anatomical and physiological factors influencing particle deposition and retention, were discussed in depth in the 1996 PM AQCD. Thus, in this chapter, only an overview of basic information related to one critical factor in deposition, namely particle size, is provided (Section 6.1.1), so as to allow the reader to understand the different terms used in the remainder of this chapter and in subsequent ones dealing with health effects. This is followed, in Section 6.1.2, by a basic overview of respiratory tract structure as it relates to the deposition evaluation. The ensuing major sections of this chapter provide updated information on particle deposition, clearance, and retention in the respiratory tract of humans, as well as laboratory animals, which are useful in the evaluation of PM health effects. Issues related to the phenomenon of particle overload as it may apply to human exposure and the use of instillation of particle suspensions as an exposure technique to evaluate PM health effects also are discussed. The final sections of the chapter deal with mathematical models of particle disposition in the respiratory tract.

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

6.1.1 Size Characterization of Inhaled Particles

Information about particle size distribution is important in the evaluation of effective inhaled dose. Particle attributes, as well as some general definitions important in understanding particle fate within the respiratory tract, are described in Chapter 2.

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

6.1.2 Structure of the Respiratory Tract

A detailed discussion of respiratory tract structure was provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996), and only a brief synopsis is presented here. For dosimetry purposes, the respiratory tract can be divided into three regions (Figure 6-1): (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists

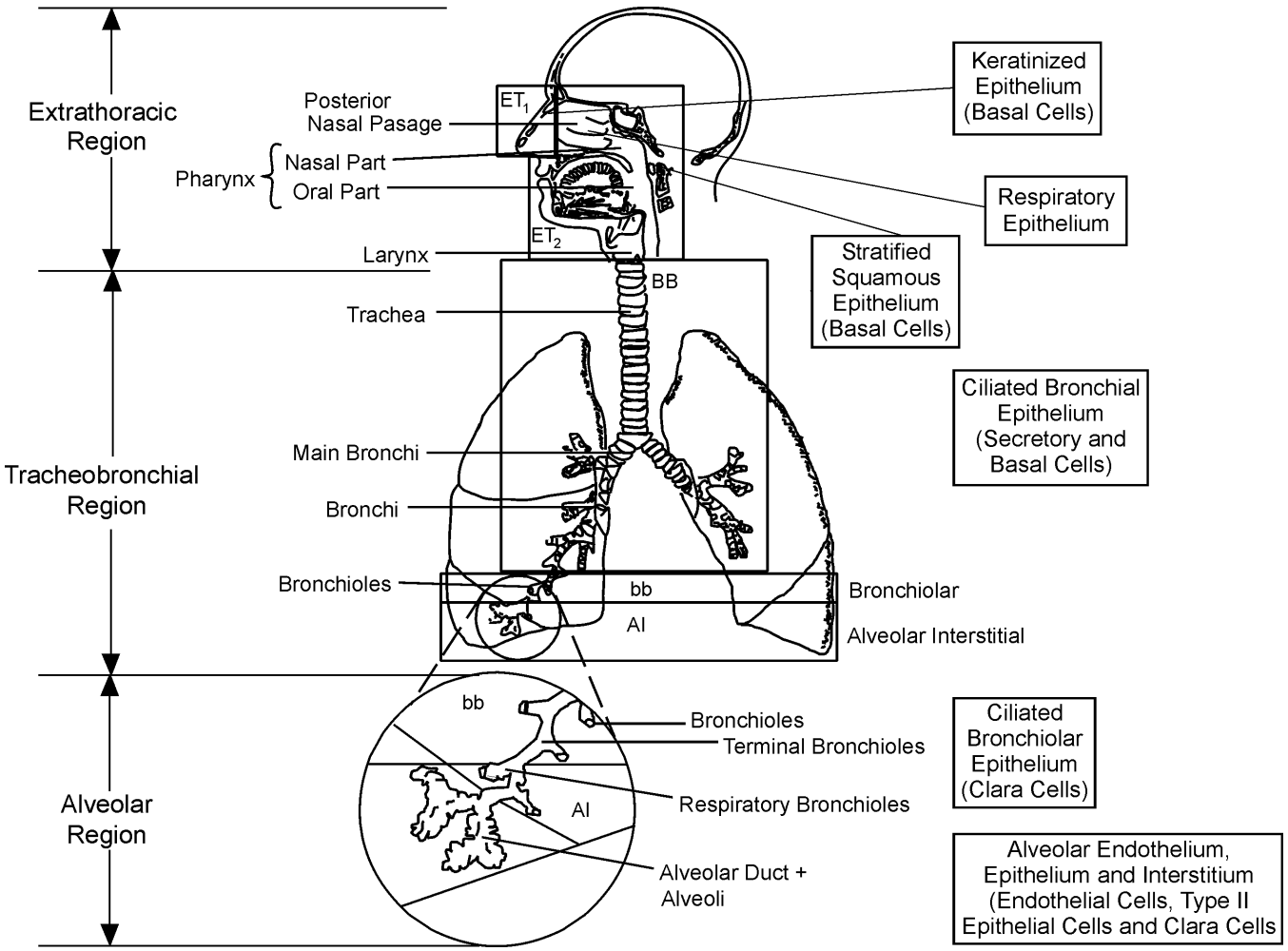

Figure 6-1. Diagrammatic representation of respiratory tract regions in humans.

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

DRAFT-DO NOT QUOTE OR CITE

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 both, known as oronasal breathing). However, most laboratory animals commonly used in respiratory toxicological studies are obligate nose breathers.

From the ET region, inspired air enters the TB region at the trachea. From the level of the trachea, the conducting airways then undergo dichotomous branching for a number of generations. The terminal bronchiole is the most peripheral of the distal conducting airways and, in humans, leads to the gas-exchange region, which consists of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (all of which comprise the A region). All of the conducting airways, except the trachea and portions of the mainstem bronchi, are surrounded by parenchymal tissue composed primarily of the alveolated structures of the A region and associated blood and lymphatic vessels. It should be noted that the respiratory tract regions are comprised of various cell types and that there are distinct differences in the distribution of cells lining the airway surfaces in the ET, TB, and A regions. Although a discussion of cellular structure of the respiratory tract is beyond the scope of this section, details may be found in a number of sources (e.g., Crystal et al., 1997).

6.2 PARTICLE DEPOSITION

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

6.2.1 Mechanisms of Deposition

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

Sudden changes in airstream direction and velocity may cause some particles to fail to follow the streamlines of airflow. As a consequence, the particles contact, or impact, airway surfaces. The ET and upper TB airways are characterized by high air velocities and sharp

directional changes and, thus, dominate as sites of inertial impaction. Impaction is a significant deposition mechanism for particles larger than 2 μm aerodynamic equivalent diameter (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: inertial impaction dominates in the upper airways, and gravitational settling becomes increasingly dominant in the smaller conducting airways.

Particles having actual physical diameters < 1 μm are subjected increasingly to diffusive deposition because of random bombardment by air molecules, resulting in contact with airway surfaces. The root mean square displacement that a particle experiences in a unit of time along a given cartesian coordinate is a measure of its diffusivity. The density of a particle is unimportant in determining 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.

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

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

Electrostatic precipitation is deposition related to particle charge. The minimum charge an aerosol particle can have is zero. This condition rarely is achieved because of the random charging of aerosol particles by air ions. Aerosol particles acquire charges by collisions with air ions because of their random thermal motion. Many laboratory-generated aerosols are highly charged and there are methods such as passage of the particle-containing airstream through a Kr-85 charge neutralizer that eliminates the charge. In addition, these aerosols will generally

lose their initial charge as they attract oppositely charged ions, and an equilibrium state of these competing processes eventually is achieved. This Boltzmann equilibrium represents the charge distribution of an aerosol in charge equilibrium with bipolar ions. The minimum amount of charge is very small: there is a statistical probability that some particles within the aerosol will have no charge and that others will have one or more positive and negative charges.

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

6.2.2 Deposition Patterns in the Human Respiratory Tract

Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition therein is necessary for understanding and interpreting the health effects associated with exposure to particles. Particles deposited in the various respiratory tract regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times. This section summarizes concepts of particle deposition in humans and laboratory animals as reported in the 1996 PM AQCD (U.S. Environmental Protection Agency, 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. Additionally, there is no lower limit to inhalability, so long as the particle exceeds a critical size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties in contrast to those of free ions or gas molecules.

6.2.2.1 Total Respiratory Tract Deposition

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

Besides particle size, breathing pattern (tidal volume, breathing frequency, route of breathing) is the most important factor affecting lung deposition. Kim (2000) reported total lung deposition values in healthy adults for a wide range of breathing patterns, tidal volumes (375 to

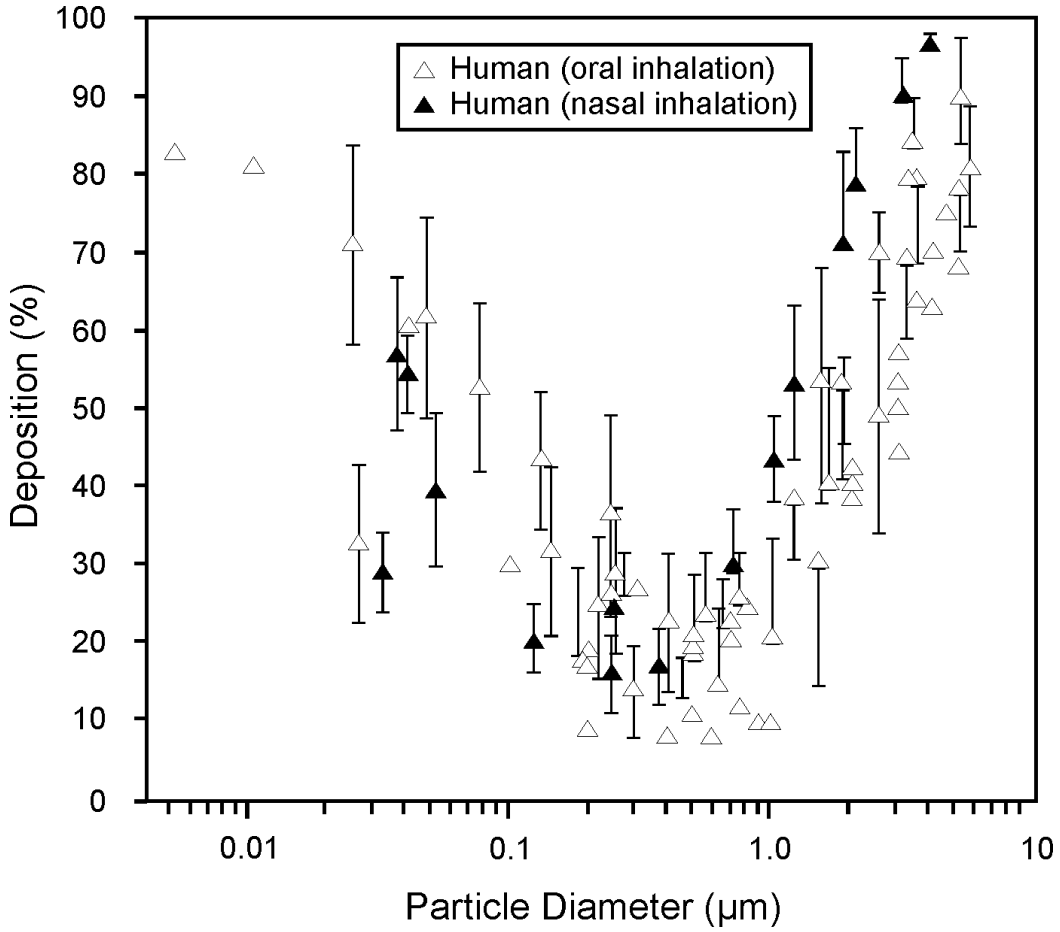

Figure 6-2. Total respiratory tract deposition (as percentage deposition of amount inhaled) in humans as a function of particle size. All values are means with standard deviations when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 μm.

Source: Modified from Schlesinger (1989).

1500 mL), flow rates (150 to 1000 mL/s), and respiratory times (2 to 12 s). Total lung deposition increased with increasing tidal volume at a given flow rate and with increasing flow rate at a given respiratory time. Various deposition values were correlated with a single composite parameter consisting of particle size, flow rate, and tidal volume.

The ultrafine mode (i.e., particles having diameters < 0.1 μm) is specifically being evaluated for determination of its potential toxicity. There is, however, little information on total respiratory tract deposition of such particles. Frampton et al. (2000) exposed healthy adult

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

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

A property of some ambient particulate species that affects deposition is hygroscopicity, the propensity of a material for taking up and retaining moisture under certain conditions of humidity and temperature. Ambient fine particles (sulfate, nitrate, and possibly organics) tend to

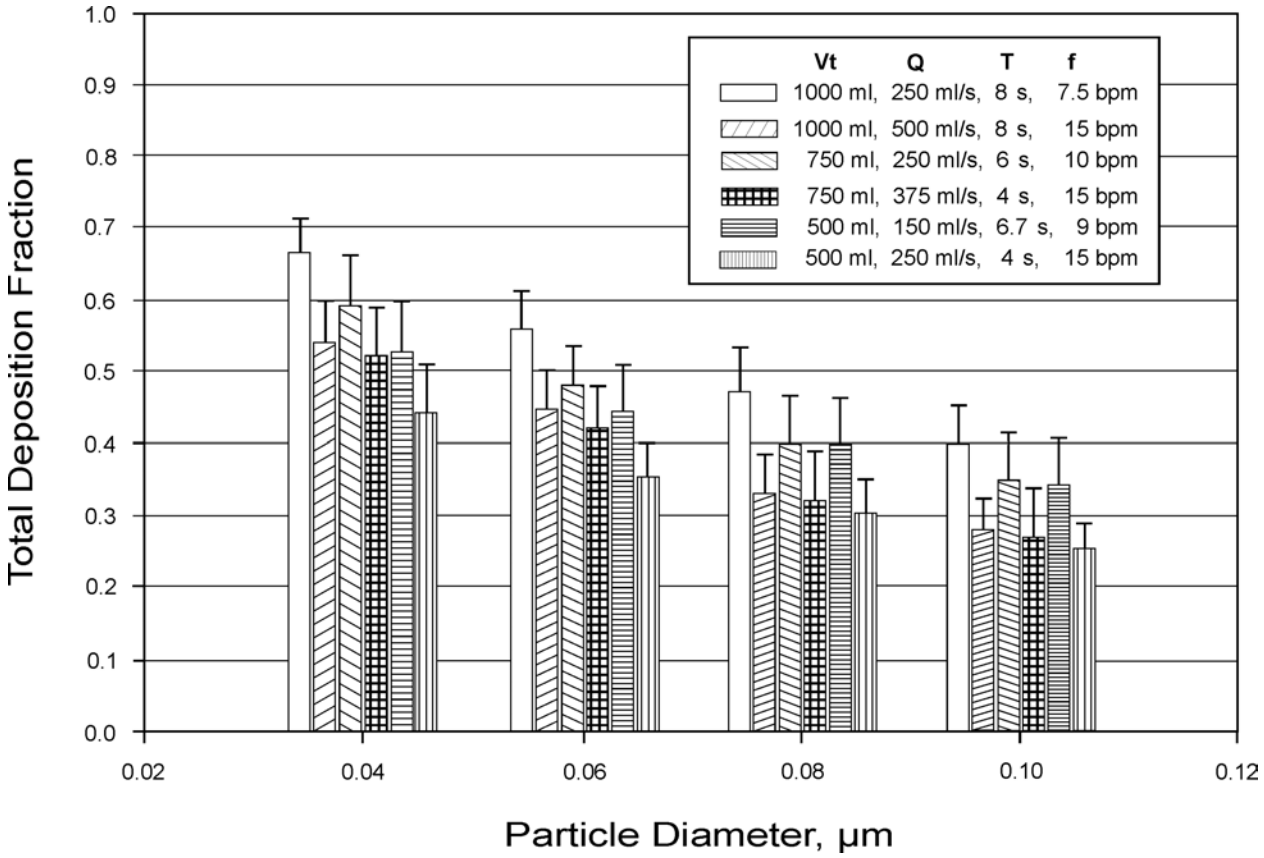

Figure 6-3. Total deposition fraction as a function of particle size in 22 healthy men and women under six different breathing patterns. For each breathing pattern, the total deposition fraction is different ($p < 0.05$) for two successive particle sizes. V_t is tidal volume (mL); Q is respiratory flow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

Source: Jacques and Kim (2000).

be hygroscopic (see Chapter 2). Such particles can increase in size in the humid air within the respiratory tract and, when inhaled, will deposit according to their hydrated size rather than their initial size. The implications of hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller (1991); whereas the difficulties of studying lung deposition of hygroscopic aerosols have been reviewed recently by Kim (2000). In general, compared to nonhygroscopic particles of the same initial size, the deposition of hygroscopic aerosols in different regions of the lung may be higher or lower, depending on the initial size.

Thus, for particles with initial sizes larger than ≈0.5 μm, the influence of hygroscopicity would be to increase total deposition with a shift from peripheral to central or extrathoracic regions; whereas for smaller ones total deposition would tend to be decreased. See Chapter 2 for a detailed description of particle hygroscopicity.

6.2.2.2 Deposition in the Extrathoracic Region

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

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

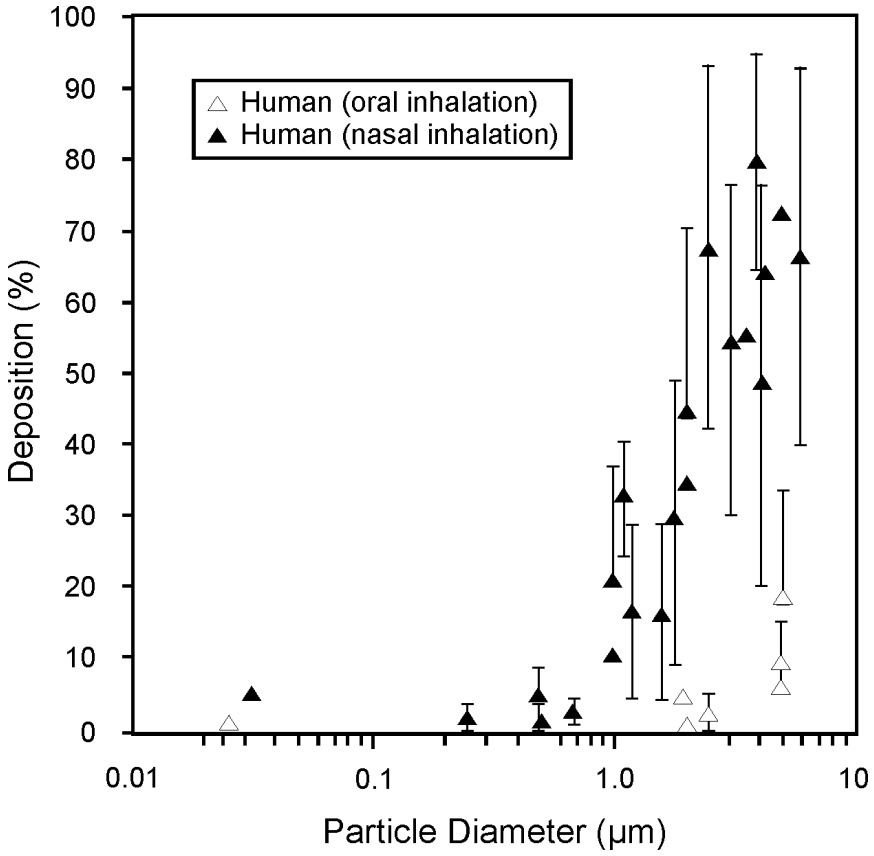

Figure 6-4. Extrathoracic deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those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

Source: Modified from Schlesinger (1989).

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

deposition in the model than did oral inhalation. These results are consistent with other studies discussed in the 1996 PM AQCD and with the known dominance of impaction deposition within the ET region.

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

For ultrafine particles ($d_p < 0.1$ μm), deposition in the ET region is controlled by diffusion, which depends only on the particle's geometric diameter. Prior to 1996, ET deposition for this particle size range had not been studied extensively in humans, and this remains the case. In the 1996 PM AQCD, the only data available for ET deposition of ultrafine particles were from hollow airway cast studies. More recently, deposition in the ET region was examined using mathematical modeling. Three- dimensional numerical simulations of flow and particle diffusion in the human upper respiratory tract, which included the nasal region, oral region, larynx, and first two generations of bronchi, were performed by Yu et al. (1998). Deposition of particles of 0.001 and 0.01 μm in these different regions was calculated under inspiratory and expiratory flow conditions. Deposition efficiencies in the total model were lower on expiration than inspiration although values for the former were quite high. About 75% of the ultrafine particles were deposited. Nasal deposition accounted for up to 54% of total deposition in the model system for 0.001-μm particles. With oral breathing, deposition efficiency was estimated at 48% (of amount entering; Yu et al., 1998).

Swift and Strong (1996) examined the deposition of ultrafine particles, ranging in size from 0.053 to 0.062 μm, in the nasal passages of normal adults during constant inspiratory flows of 6 to 22 L/min. The results are consistent with results noted in studies above, namely that the nasal passages are highly efficient collectors for ultrafine particles. In this case, fractional deposition ranged from 94 to 99% (of amount inhaled). Only a weak dependence of deposition on flow rate was found, which contrasts with results noted above (i.e., Lennon et al., 1998) for particles > 0.3 μm, but is consistent with diffusion being the main deposition mechanism. This report has important implications for assessing the toxicity of PM because the filtration

efficiency of the nasal passages will lessen the probability of ultrafine particle deposition in the lungs.

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

The results of all of the above studies support the previously known ability of the ET region, especially the nasal passages, to act as an efficient filter for nanoparticles (< 0.1 μm) as well as for larger ones (> 5 μm), potentially reducing the amount of particles within a wide size range that are available for deposition in the TB and A regions.

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

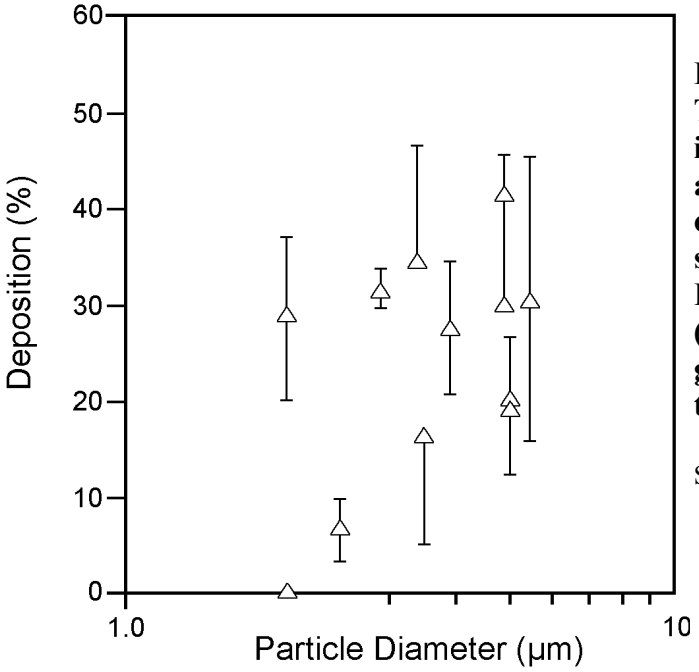

Figure 6-5.
Tracheobronchial deposition (oral inhalation as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.05 µm and geometric (or diffusion equivalent) for those < 0.5 µm.

Source: Modified from Schlesinger (1989).

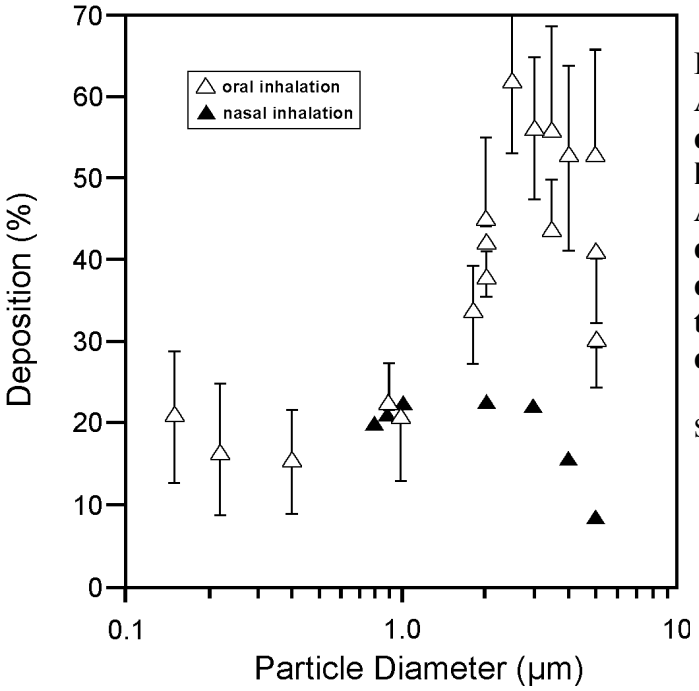

Figure 6-6.
Alveolar deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.05 µm and geometric (or diffusion equivalent) for those < 0.5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

Source: Modified from Schlesinger (1989).

uses nonradioactive aerosols and can estimate regional deposition in a virtually unlimited number of lung compartments. Because of experimental limitations of the technique, the investigators estimated regional lung deposition in ten serial, 50-mL increments from the mouth to the end of a typical 500-mL tidal volume. Deposition estimates in the TB and A regions were obtained for both men and women for particles ranging from 0.04 to 5.0 μm in diameter. It should be noted that particle deposition in the TB and A regions was based on volumetric compartments of 50- to 150-mL and > 150 mL, respectively. Deposition in the ET region was based on the 0- to 50-mL compartment. Lung deposition fractions are shown in Figure 6-7. In men, 24-32% of total particle deposition (0.04-, 0.06-, 0.08-, and 0.10-μm particles) was deposited in the TB region and 67-76% was deposited in the A region. In women, deposition of these particles was consistently greater in the TB region (21-48%), but was comparable or slightly smaller in the A region as compared to men. As a result, total lung deposition of ultrafine particles was slightly greater in women than men (~5-14%). For 1-, 3-, and 5-μm particles, 16-37% of total particle deposition, in men, was deposited in the TB region and 57-83% was deposited in the A region. Deposition of these size particles was consistently greater in the TB region in women (27-68%), but was comparable or slightly smaller in the A region as compared to men. As a result, total lung deposition was slightly greater in women than men (~16-22%). Thus, deposition of ultrafine and coarse particles in the TB region was greater for women than men.

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

Brody and Roe (1983) studied the deposition pattern of 5 aerosolized dusts (chrysotile and crocidolite asbestos, fiber glass, α-quartz, and ash from Mt. St. Helens) in the lungs of rats. Mice were exposed to chrysotile asbestos. Quantitative electron microscopy was carried out on tissues fixed by vascular perfusion. Immediately following a brief exposure, a significantly greater number of particles had deposited on alveolar duct bifurcations when compared with the number of particles on duct surfaces adjacent to the bifurcations. Few particles were counted at midpoints between bifurcations, and particles were rarely observed within alveoli. The data show that regardless of mineral nature, shape, or concentration, inhaled particles small enough to

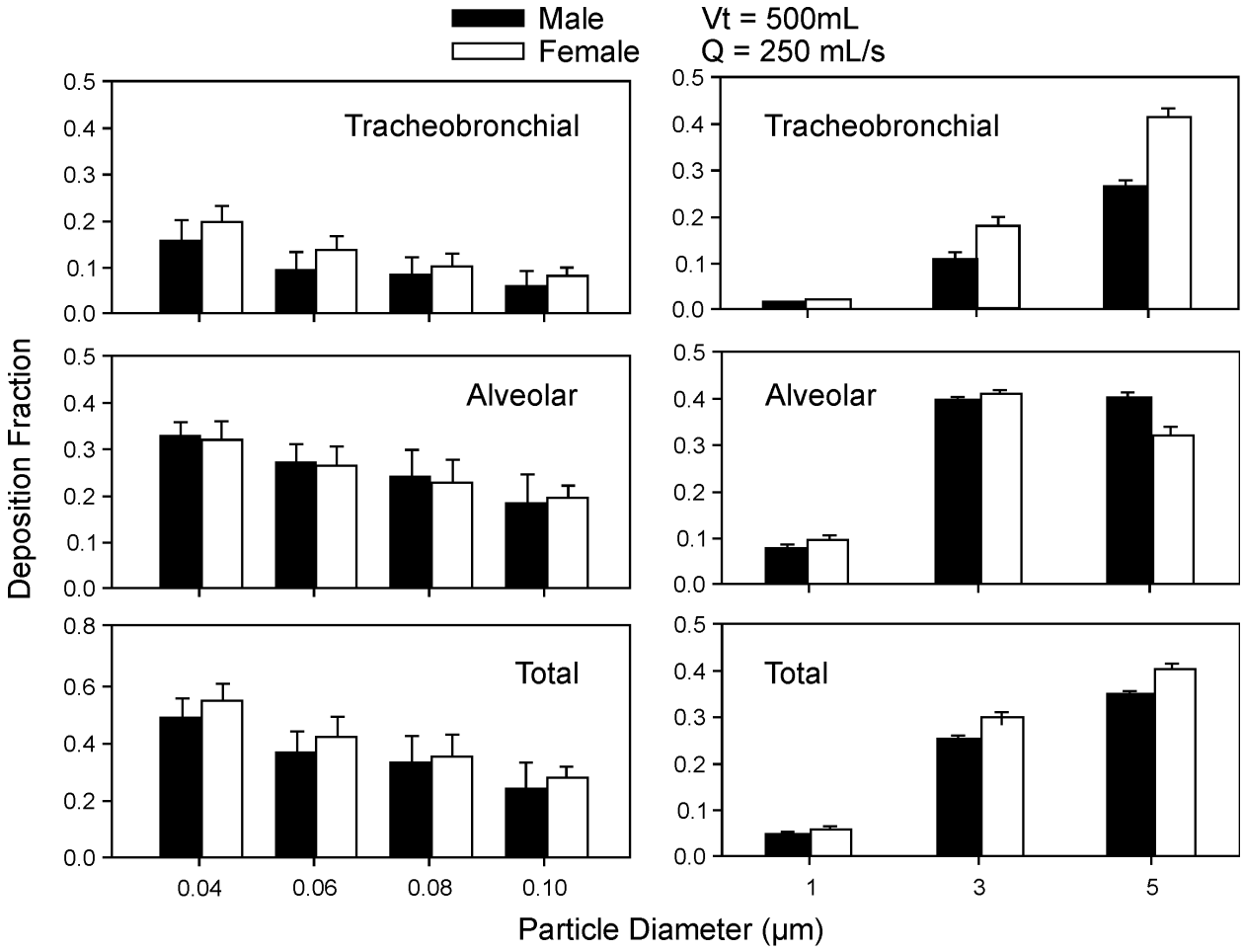

Figure 6-7. Lung deposition fractions in the tracheobronchial (TB) and alveolar (A) regions estimated by the bolus technique. Using a breathing pattern of 500 mL at 15 breaths per min, TB deposition was 1.5, 10.6, and 26.1% and A deposition was 7.7, 39.4, and 39.8% for particles of 1, 3, and 5 µm in diameter, respectively, for men. In comparison to men, TB deposition in women was 27-68% greater, whereas A deposition was comparable. For ultrafine particles of 0.04 to 0.1 µm diameter, TB and A deposition in men ranged from 5.7 to 15.6% and 18.2 to 33.1%, respectively. In comparison to men, TB deposition was 21-48% greater, whereas A deposition was comparable. 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).

pass through the conducting airways are deposited primarily at alveolar duct bifurcations. The authors proposed that the alveolar deposition patterns are the result of airflow characteristics that cause enhanced deposition of particles at alveolar duct bifurcations intersecting the flow and is similar to deposition patterns that occur at bifurcations of conducting airways.

Brody et al. (1981) studied the initial deposition and subsequent translocation of chrysotile asbestos in the lungs of rats exposed for 1 h. Using scanning and transmission electron microscopy of tissue fixed by vascular perfusion, they determined that the majority of fibers that pass through the conducting airways deposit at the bifurcations of alveolar ducts. The farther an alveolar duct bifurcation was from its terminal bronchiole, the less asbestos was observed.

Warheit and Hartsky (1990) compared inhaled-particle-deposition patterns in alveolar regions of four rodent species with differing airway branching patterns and poorly developed respiratory bronchioles. Proximal alveolar regions of hamsters and guinea pigs contain rudimentary respiratory bronchioles; whereas in rats and mice, terminal bronchioles lead directly into alveolar ducts. Groups of animals from one strain each of rats, mice, hamsters, and guinea pigs were exposed to aerosols of carbonyl iron (CI) particles (100 mg/m^3) for 1 h. Total lung deposition of iron particles was highest in mice and hamsters. Particle deposition patterns in the proximal regions of the distal lung were similar for all species although greater numbers of CI particles per bifurcation were deposited in rats and mice compared to hamsters, and greater numbers were deposited in hamsters compared to guinea pigs. The data suggest that the presence of undeveloped respiratory bronchioles in the lungs of hamsters and guinea pigs has little influence on distal lung particle deposition patterns. It is not known whether inhaled particles are deposited at similar sites in the lungs of species with well-developed respiratory bronchioles such as cats, nonhuman primates, and humans.

6.2.2.4 Local Distribution of Deposition

Airway structure and its associated air flow patterns are exceedingly complex, and ventilation distribution of air in different parts of the lung is uneven. Thus, it is expected that particle deposition patterns within the ET, TB, and A regions would be highly nonuniform, with some sites exhibiting deposition that is much greater than average levels within these regions. This was discussed in detail in the 1996 PM AQCD. Basically, using deposition data from living subjects as well as from mathematical and physical models, enhanced deposition has been shown

to occur in the nasal passages and trachea and at branching points in the TB and A regions (see Chapter 10 of U.S. Environmental Protection Agency, 1996). Churg and Vedal (1996) examined retention of particles on carinal ridges and tubular sections of airways from lungs obtained at necropsy. Results indicated significant enhancement of particle retention on carinal ridges through the segmental bronchi; the ratios were similar in all airway generations examined.

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

Comer et al. (2000) used a three-dimensional computer simulation technique to investigate local deposition patterns in sequentially bifurcating airway models that were previously used in experiments by Kim and Fisher (1999). The simulation was for 3-, 5-, and 7-μm particles and assumed steady, laminar, constant air flow with symmetry about the first bifurcation. The overall trend of the particle deposition efficiency, i.e., an exponential increase with Stokes number, was similar for all bifurcations; and deposition efficiencies in the bifurcation regions agreed very well with experimental data. Local deposition patterns consistently showed that the majority of the deposition occurred within the carinal region.

Deposition "hot spots" at airway bifurcations have undergone additional analyses using mathematical modeling techniques. Using calculated deposition sites, a strong correlation has been demonstrated between secondary flow patterns and deposition sites and density both for large (10 μm) particles and for ultrafine particles (0.01 μm; Heistracher and Hofmann, 1997;

Hofmann et al., 1996). This supports experimental work, noted in U.S. Environmental Protection Agency (1996), indicating that, like larger particles, ultrafine particles also show enhanced deposition at airway branch points — even in the upper tracheobronchial tree.

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

Bennett et al. (1998) studied the effect of variable anatomic dead space (ADS) on aerosol bolus delivery in healthy subjects inhaling radiolabeled, ^{99m}Tc-iron oxide particles (3.5 μm). The subjects inhaled 40 mL aerosol boluses to a volumetric front depth of 70 mL into the lung at a lung volume of 70% total lung capacity end-inhalation and estimated the fraction of the inhaled boluses deposited in intrathoracic airways (IDF). ADS was also measured from 70% total lung capacity. The IDF deposition fraction varied from 0.04 – 0.43 and increased with decreasing ADS. The deposited dose in the IDF was lower in subjects with large ADS (> 250 mL). A lower dose to the IDF was also noted in women due to a smaller IDF and smaller airspace dimensions. They observed significantly greater deposition in the left (L) versus right lungs (R); mean L/R (ratio of deposition in L lung to R lung, normalized to ratio of L-to-R lung volume) was 1.58 ± 0.42. Retention of deposited particles at 2 h was independent of ADS or IDF. There was significant retention of particles in the whole lung at 24 h post deposition and slow clearance of these particles continued through 48 h post deposition. There was significant retention of insoluble particles in large bronchial airways at 24 h post deposition (i.e., 24 h central-to-peripheral ratio = 1.40 and 1.82 in the R and L lung, respectively).

Kim and Jaques (2000) used the respiratory bolus technique to estimate the deposition distribution of ultrafine particles (0.04, 0.06, 0.08, and 0.1 μm) in young adults. Under normal breathing conditions (tidal volume 500 mL, respiratory flow rate 250 mL/s), bolus aerosols were delivered sequentially to a lung depth ranging from 50 to 500 mL in 50-mL increments. The

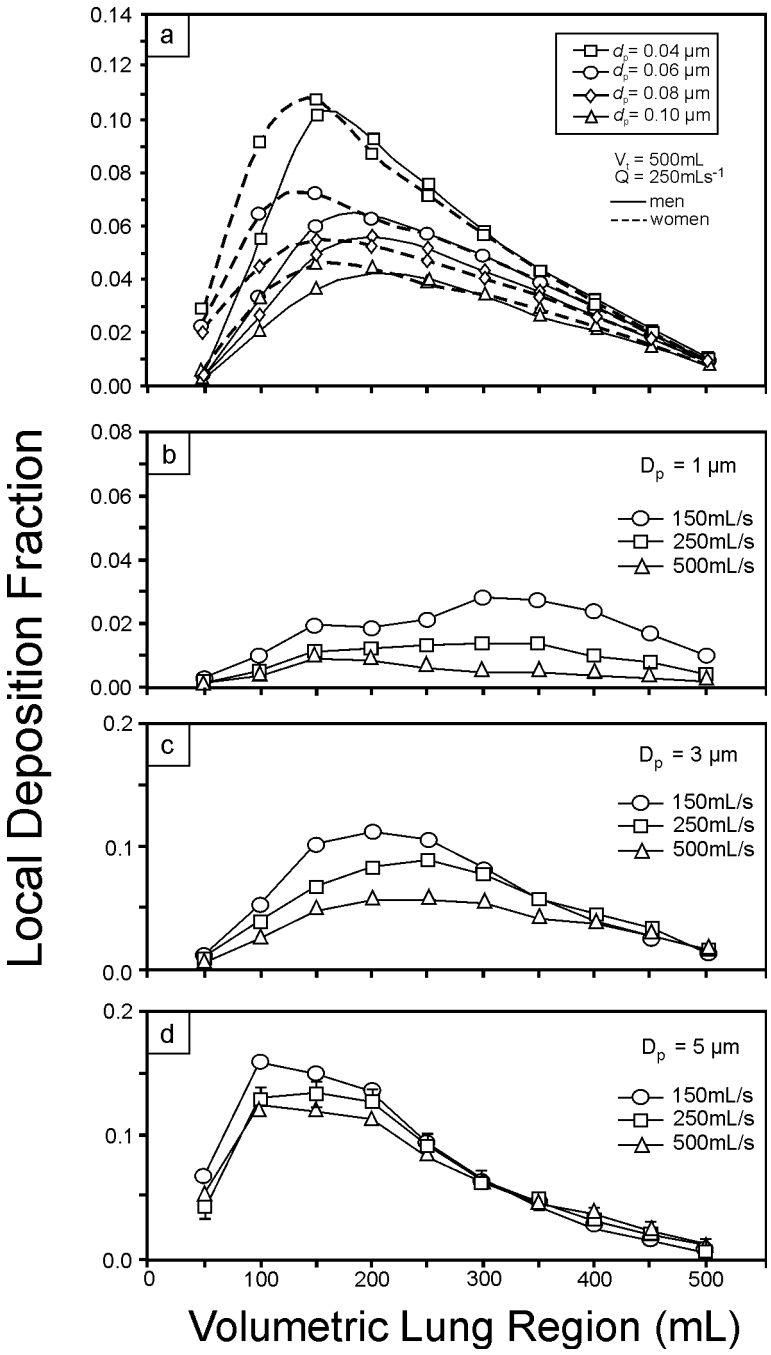

Figure 6-8. Estimated lung deposition fractions in ten volumetric regions for particle sizes ranging from ultrafine particle diameter (d_p) of 0.04 to 0.01 µm (Panel A) to fine (d_p = 1.0 µm; Panel B) and coarse (d_p = 3 and 5 µm; Panels C and D). Healthy young adults inhaled a small bolus of monodisperse 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 Jaques (2000).

results indicate that regional deposition of ultrafine particles (0.4-1.0 μm) varies widely along the depth of the lung. Regional deposition of larger particles (1.0-5.0 μm) is far less variable (Figure 6-8). The deposition patterns for ultrafine particles, especially for very small ultrafine particles, were similar to those for coarse particles. Peak deposition occurred in the lung regions situated between 150 and 200 mL from the mouth, and sites of peak deposition shifted proximally with decreasing particle size. Deposition dose per unit average surface area was greatest in the proximal lung regions and decreased rapidly with increased lung depth. Peak surface dose was 5 to 7 times greater than average lung dose. These results indicate that local enhancement of dose occurs in healthy lungs, which could be an important factor in eliciting pathophysiological effects.

6.2.2.5 Deposition of Specific Size Modes of Ambient Aerosol

Several recent modeling studies provide estimates of the deposition profiles of "real world" particle size fractions. One such study using a lung-anatomical model (Venkataraman and Kao, 1999) examined the contribution of two specific size modes of the PM_{10} ambient aerosol, namely the fine mode (defined as particles with diameters up to 2.5 μm) and the thoracic fraction of the coarse mode (defined as particles with diameters 2.5 to 10 μm) to total lung and regional lung doses (i.e., a daily dose expressed as μg/day, and a surface dose expressed a $\mu g/cm^2$/day) resulting from a 24-h exposure to a particle concentration of 150 $\mu g/m^3$. The study also evaluated deposition in terms of two metrics, namely mass dose and number dose. Deposition was calculated using a mathematical model for a healthy human lung under both simulated moderate exertion (1 L at 15 breaths/min) and vigorous exertion (1.5 L at 15 breaths/min) and for a compromised lung (0.5 L at 30 breaths/min). Regional deposition values were obtained for the ET, TB, and A regions. Because the exposure scenario used is quite unrealistic, only general trends should be inferred from this study rather than actual deposition values. These estimates would also be highly uncertain for the compromised lung.

The daily modeled mass dose peaked in the A airways for all breathing patterns; whereas that for the coarse fractions was comparable in the TB and A regions. The mass per unit surface area of various airways from the fine and coarse fractions was larger in the trachea and first few generations of bronchi. It was suggested that these large surface doses may be related to aggravation of upper respiratory tract illness.

The modeled daily number dose was different for fine and coarse fractions in all lung airways: the dose from the fine fraction was higher by about 100 times in the ET and about 10^5 times in internal lung airways. The surface number dose (particles/cm^2/day) was 10^3 to 10^5 times higher for fine than for coarse particles in all lung airways, indicating the larger number of fine particles depositing. Particle number doses did not follow trends in mass doses and are much higher for fine than coarse particles and are higher for different breathing patterns. It also was concluded that the fine fraction contributes 10,000 times greater particle number per alveolar macrophage than the coarse fraction particles. As noted, these results must be viewed with caution because they were obtained using a pure mathematical model that must be validated in terms of realistic physiologic conditions.

Another evaluation of deposition that included consideration of size mode of the ambient aerosol was that of Broday and Georgopoulos (2001). In this case, a mathematical model was used to account for particle hygroscopic growth, transport, and deposition in tracking the changes in the size distribution of inhaled aerosols. It was concluded that different rates of particle growth in the inspired air resulted in a change in the aerosol size distribution such that increased mass and number fractions of inspired ultrafine particles (< 0.1 μm) were found in the size range between 0.1 to 1 μm and, therefore, deposited to a lesser extent due to a decrease in diffusion deposition. On the other hand, particles that were originally in the 0.1- to 1-μm size range when inhaled will undergo enhanced deposition because of their increase in size resulting from hygroscopic growth. Hence, the initial size distribution of the inhaled polydisperse aerosol affects the evolution of size distribution once inhaled and, thus, its deposition profile in the respiratory tract. Hygroscopicity of respirable particles must be considered for accurate predictions of deposition. Because different size fractions likely have different chemical composition, such changes in deposition patterns will affect biological responses.

6.2.3 Biological Factors Modulating Deposition

Experimental deposition data in humans have been commonly derived using healthy adult Caucasian males. Various factors can act to alter deposition patterns from those obtained in this group. Evaluation of these factors is important to help understand potentially susceptible subpopulations because differences in biological response following pollutant exposure may be caused by dosimetry differences as well as by differences in innate sensitivity. The effects of

different biological factors on deposition were discussed in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) and are summarized below together with additional information obtained from more recent studies.

6.2.3.1 Gender

Males and females have different body size, conductive airway size, and ventilatory parameter distributions; therefore, it is expected that there would be gender differences in deposition. In some of the controlled studies, however, men and women are breathing at the same tidal volume and frequency. If the women are generally smaller than the men, the increased minute ventilation compared to their normal ventilation would cause different changes in deposition patterns. In these cases, it would be better for the investigators to have used size-adjusted tidal volumes. This may help to explain some of the differing results discussed below.

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

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

Kim and Hu (1998) assessed regional deposition patterns in healthy adult males and females using particles with median aerodynamic sizes of 1, 3, and 5 μm and a bolus delivery technique that involved controlled breathing. The total fractional deposition in the lungs was similar for both genders with the smallest particle size, but was greater in women for the 3- and 5-μm particles regardless of the inhalation flow rate used; this difference ranged from 9 to 31%, with higher values associated with higher flow rates. The pattern of deposition was similar for both genders although females showed enhanced deposition peaks for all three particle sizes.

The volumetric depth location of these peaks was found to shift from peripheral (i.e., increased volumetric depth) to proximal (i.e., shallow volumetric depth) regions of the lung with increasing particle size, but the shift was greater in females than in males. Thus, deposition appeared to be more localized in the lungs of females compared to those of males. These differences were attributed to the smaller size of the upper airways, particularly of the laryngeal structure, in females. Local deposition of 1-μm particles was somewhat flow dependent but, for larger (5-μm) particles, was largely independent of flow (flows did not include those that would be typical of exercise).

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

Jaques and Kim (2000) and Kim and Jaques (2000) expanded the evaluation of deposition in males and females to particles < 1 μm. They measured total fractional lung deposition in healthy adults using sizes in the ultrafine mode (0.04 to 0.1 μm) in addition to those having diameters of 1 and 5 μm. Total fractional lung deposition was greater in females than in males for 0.04- and 0.06-μm particles. The difference was negligible for 0.08- and 0.1-μm particles. Therefore, the gender effect was particle-size dependent, showing a greater fractional deposition in females for very small ultrafine and large coarse particles, but not for particles ranging from 0.08 to 1 μm. A local deposition fraction was determined in each volumetric compartment of the lung to which particles are injected based on the inhalation procedure (Kim and Jaques, 2000). The fractional deposition was found to increase with increasing lung depth from the mouth, reach a peak value, and then decrease with further increase in lung volumetric depth. The height of the peak and its depth varied with particle size and breathing pattern. Peak fractional

deposition for the 5-μm particles was more proximal than that for the 1-μm particles; whereas that for the ultrafine particles occurred between these two peaks. For the ultrafine particles, the peak fractional deposition became more proximal as particle size decreased. Although this pattern of deposition distribution was similar for both men and women, the region of peak fractional deposition was shifted closer to the mouth and peak height was slightly greater for women than for men for all exposure conditions.

6.2.3.2 Age

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

Modeled Deposition Patterns

Potential regional deposition differences between children and adults have been assessed to a greater extent using mathematical models. These indicated that, if the entire respiratory tract and a complete breathing cycle at normal rate are considered, then ET deposition in children would be generally higher than that in adults. However, TB and A regional deposition in children may be either higher or lower than that in adults, depending on particle size (Xu and Yu, 1986). There is enhanced TB deposition in children for particles < 5 μm (Xu and Yu, 1986; Hofmann et al., 1989a). Becquemin et al. (1991) compared nasal filtering efficiency in children and adults; two groups of children (12 children, aged 5.5-11.5 y; 8 children, aged 12-15 y) were studied along with 10 adults. The deposition of polystyrene beads (1, 2.05, 2.8 μm MMAD) was measured for both nose and mouth breathing. Ventilation was controlled to scale breathing patterns appropriate for each age either at rest or during moderate exercise. Anterior nasal resistance and standard lung function were measured for each subject. For the same inhalation flow rate, children had much higher nasal resistances than adults. Individually, nasal deposition increased with particle size, ventilation flow rate and nasal resistance, from rest to exercise.

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

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

CF = Cystic fibrosis.

DRAFT-DO NOT QUOTE OR CITE

The average nasal deposition percentages were lower in children than in adults at rest; these differences were even greater during exercise. The average nasal deposition percentages in children and in adults for these particle sizes were better correlated with inspiratory airflow rate than with resistances or pressure drops at rest and during moderate exercise. The authors conclude that while the airways of children are narrower, they are also shorter and the inhalation flow rate is reduced. This would mean that the thoracic airways of children are protected to a lesser degree than those of adults.

An age dependent theoretical model to predict regional particle deposition in children's lungs that incorporates breathing parameters and morphology of the growing lung was developed by Musante and Martonen (1999). The model was used to compare deposition of monodisperse aerosols, ranging from 0.25 to 5 μm, in the lungs of children (ages 7, 22, 48, and 98 mo) at rest to that in adults (ages 30 years) at rest. Compared to adults, fractional deposition was highest in the 48- and 98-mo subjects for all particle sizes; TB fractional deposition was found to be a monotonically decreasing function of age for all sizes; and total fractional lung deposition (i.e., TB+A) was generally higher in children than adults, with children of all ages showing similar total deposition fractions.

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

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

Cheng et al. (1995) examined deposition of ultrafine particles in replica casts of the nasal airways of children aged 1.5 to 4 years. Particle sizes ranged from 0.0046 to 0.2 μm, and both

inspiratory and expiratory flow rates were used (3 to 16 L/min). Deposition efficiency was found to decrease with increasing age for a given particle size and flow rate.

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

Inhaled Deposition Patterns

Bennett et al. (1997a) analyzed the regional deposition of poorly soluble 4.5-μm particles inhaled via mouthpiece. The subjects were children and adults with mild cystic fibrosis (CF), but who likely had normal upper airway anatomy such that intra- and extrathoracic deposition would be similar to that in healthy people. The mean age of the children was 13.8 years and 29.1 years for the adults. Extrathoracic deposition of the 4.5-μm particles, as a percentage of total respiratory tract deposition, was higher by about 50% in children compared to adults (30.7%, 20.1%, and 16.0%, respectively). There was an age dependence of ET deposition for the 4.5-μm particles in the children in that the percentage ET deposition tended to be higher at a younger age ($p = 0.08$); the younger group (< 14 years; $p = 0.05$) had almost twice the percentage ET deposition of the older group (> 14 years). Additional analyses showed an inverse correlation of extrathoracic deposition with body height. There was no significant difference in lung or total respiratory tract deposition between the children and adults. Because ET deposition was age dependent and total deposition was not, this suggests that, in children, the ET region does a more effective job of filtering out particles that would otherwise reach the TB region. However, because the lungs of children are smaller than are those of adults, children may still have deposition per unit surface area comparable to adults. These results are consistent with the predicted increase in head deposition of particle greater than 2 μm with decreasing age reported by Xu and Yu (1986).

Bennett and Zeman (1998) measured the deposition of monodisperse 2-μm (MMAD) particles in children (aged 7 to 14 years) and adolescents (aged 14 to 18 years) for comparison to that in adults (19 to 35 years). Each subject inhaled the particles by following their previously determined individual spontaneous resting breathing pattern. Deposition was assessed by

measuring the amount of particles inhaled and exhaled. There was no age-related difference in deposition within the children group. There was also no significant difference in deposition between the children and adolescents between the children and adults or between the adolescents and adults. However, the investigators noted that, because the children had smaller lungs and higher minute volumes relative to lung size, they likely would receive greater doses of particles per lung surface area compared to adults. Furthermore, breath-to-breath fractional deposition in children did vary with tidal volume, increasing with increasing volume. The rate of deposition normalized to lung surface area tended ($p = 0.07$) to be greater (35%) in children when compared to the combined group of adolescents and adults. These additional studies still do not provide unequivocal evidence for significant differences in deposition between adults and children, even when considering differences in lung surface area. However, it should be noted that differences in levels of activity between adults and children are likely to play a fairly large role in age-related differences in deposition patterns of ambient particles. Children generally have higher activity levels during the day and higher associated minute ventilation per lung size, which can contribute to a greater size-specific dose of particles. Activity levels in relationship to exposure are discussed more fully in Chapter 5.

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

6.2.3.3 Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that occurring in healthy individuals. The effect of airway diseases on deposition has been studied extensively, as described in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996). Studies described therein showed that people with chronic obstructive pulmonary disease (COPD) had very heterogeneous deposition patterns and differences in regional deposition compared to normals. People with asthma and obstructive pulmonary disease tended to have greater TB deposition than did healthy people. Furthermore, there tended to be an inverse relationship between bronchoconstriction and

the extent of deposition in the A region; whereas total respiratory tract deposition generally increased with increasing degrees of airway obstruction. The described studies were performed during controlled breathing; i.e., all subjects breathed with the same tidal volume and respiratory rate. However, although resting tidal volume is similar or elevated in people with COPD compared to healthy individuals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, some of the reported differences in the deposition of particles could have been caused by increased fractional deposition with each breath. Although the extent to which lung deposition may change with respect to particle size, breathing pattern, and disease status in people with COPD is still unclear, some recent studies have attempted to provide additional insight into this issue.

Bennett et al. (1997b) measured the fractional deposition of insoluble 2-μm particles in people with severe to moderate COPD (mix of emphysema and chronic bronchitis, mean age 62 years) and compared this to healthy older adults (mean age 67 years) under conditions where the subjects breathed using their individual resting breathing pattern as well as a controlled breathing pattern. People with COPD tended to have an elevated tidal volume and a faster breathing rate than people with healthy lungs, resulting in about 50% higher resting minute ventilation. Total respiratory tract deposition was assessed in terms of deposition fraction (determined from measures of the amount of aerosol inhaled and exhaled) and deposition rate (the amount of particulate deposited per unit time). Under typical breathing conditions, people with COPD had about 50% greater deposition fraction than did age-matched healthy adults. Because of the elevation in minute ventilation, people with COPD had average deposition rates about 2.5 times that of healthy adults. Similar to previously reviewed studies (U.S. Environmental Protection Agency, 1996), these investigators observed an increase in deposition with an increase in airway resistance, suggesting that, at rest, COPD resulted in increased deposition of fine particles in proportion to the severity of airway disease. The investigators also reported a decrease in deposition with increasing mean effective airspace diameter; this suggested that the enhanced deposition was associated more with the chronic bronchitic component of COPD than with the emphysematous component. Greater deposition was noted with natural breathing compared to the fixed pattern.

Kim and Kang (1997) measured lung deposition of 1-μm particles inhaled via the mouth by healthy adults (mean age 27 years) and by those with various degrees of airway obstruction,

namely smokers (mean age 27 years), smokers with small airway disease (SAD; mean age 37 years), asthmatics (mean age 48 years), and patients with COPD (mean age 61 years) breathing under the same controlled pattern. Deposition fraction was obtained by measuring the number of particles inhaled and exhaled, breath by breath. There was a marked increase in deposition in people with COPD. Deposition was 16%, 49%, 59%, and 103% greater in smokers, smokers with SAD, asthmatics and people with COPD, respectively, than in healthy adults. Deposition in COPD patients was significantly greater than that associated with either SAD or asthma; there was no significant difference in deposition between people with SAD and asthma. Deposition fraction was found to be correlated with percent predicted forced expiratory volume (FEV_1) and forced expiratory flow ($FEF_{25-75\%}$). Airway resistance was not correlated strongly with total lung deposition. Kohlhäufl et al. (1999) showed increased deposition of fine particles (0.9 μm) in women with bronchial hyperresponsiveness.

Brown et al. (2001) examined the relationship between regional lung deposition for coarse particles (5 μm) and ventilation patterns in healthy adults and in patients with CF. They found that deposition in the TB region was positively associated with regional ventilation in healthy subjects, but negatively associated in CF patients. The relationships were reversed for deposition in the A region. These data suggest that significant coarse particle deposition may occur in the TB region of poorly ventilated lungs, as occurs in CF; whereas TB deposition follows ventilation in healthy subjects.

Segal et al. (2000a) developed a mathematical model for airflow and particle motion in the lung that was used to evaluate how lung cancer affects deposition patterns in the lungs of children. It was noted that the presence of airway tumors could affect deposition by increasing probability of inertial deposition and diffusion. The former would occur on upstream surfaces of tumors and the latter on downstream surfaces. It was concluded that particle deposition is affected by the presence of airway disease, that effects may be systematic and could be predicted, and that, therefore, they could be incorporated into dosimetry models. Segal et al. (2002) used a computer model to calculate the deposition fractions of PM within the lungs of COPD patients. The original model was for a healthy lung with a total volume of 4800 mL. The chronic bronchitis component of COPD was modeled by reducing airway diameters based on airway resistance measurements in vivo. The emphysema component was modeled by increasing alveolar volumes by 10 – 30%. The calculated results were compared with

experimental data obtained from COPD patients for controlled breathing trials (tidal volume of 500 mL, respiratory time of 1 s) with a particle size of 1 μm. The model successfully depicts PM deposition patterns and their dependence on the severity of disease and indicate that airway obstructions are the main cause for increased deposition in the COPD lung.

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

6.2.3.4 Anatomical Variability

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

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

Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size from 0.004 to 0.15 μm and at two constant inspiratory flow rates, 167 and 33 mL/s. Deposition was evaluated in relation to measures of nasal geometry as determined by magnetic resonance imaging and acoustic rhinometry. They noted that interindividual variability in deposition was correlated with the wide variation of nasal dimensions, in that greater surface

area, smaller cross-sectional area, and increasing complexity of airway shape were all associated with enhanced deposition.

Using a regression analysis of data on nasal airway deposition derived from Cheng et al. (1996), Guilmette et al. (1997) noted that the deposition efficiency within this region was highly correlated with both nasal airway surface area and volume; this indicated that airway size and shape factors were important in explaining intra-individual variability noted in experimental studies of human nasal airway aerosol deposition. Thus, much of the variability in measured deposition among people resulted from differences in the size and shape of specific airway regions.

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

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

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

Hofmann et al. (2000) examined the role of heterogeneity of airway structure in the rat acinar region in affecting deposition patterns within this area of the lungs. By the use of

different morphometric models, they showed a substantial variability in predicted particle deposition and concluded that the heterogeneity of acinar airway structure is primarily responsible for the heterogeneity of acinar particle deposition.

6.2.4 Interspecies Patterns of Deposition

The primary purpose of this document is to assess the health effects of particles in humans. As such, human dosimetry studies have been stressed. Such studies avoid uncertainties associated with extrapolation of dosimetry from laboratory animals to humans. Nevertheless, animal models have been and are currently being used in evaluations of health effects from particulate matter because there are ethical limits to the types of studies that can be performed on human subjects. Because of this, there is a considerable need to understand dosimetry in animals and to understand dosimetric differences between animals and humans. In this regard, there are a number of newly published studies that were designed to assess particle dosimetry in commonly used animals and to relate this to dosimetry in humans.

The various species used in inhalation toxicological studies that serve as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, or A) when exposed to the same aerosol at the same inhaled concentration. Such interspecies differences are important because any toxic effect is often related to the quantitative pattern of deposition within the respiratory tract as well as to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which deposited material is cleared and redistributed (Schlesinger, 1985). Differences in patterns of deposition between humans and animals were summarized previously in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) and by others (Schlesinger et al., 1997). Such differences in initial deposition must be considered when relating biological responses obtained in laboratory animal studies to effects in humans.

It is difficult to systematically compare interspecies deposition patterns obtained from various reported studies because of variations in experimental protocols, measurement techniques, definitions of specific respiratory tract regions, and so on. For example, tests with humans are generally conducted under protocols that standardize the breathing pattern; whereas those using laboratory animals involve a wider variation in respiratory exposure conditions (e.g., spontaneous breathing versus ventilated breathing or varying degrees of sedation). Much of the

variability in the reported data for individual species may be due to the lack of normalization for specific respiratory parameters during exposure. In addition, the various studies have used different exposure techniques, such as nasal mask, oral mask, oral tube, or tracheal intubation. Regional deposition is affected by the exposure route and delivery technique employed.

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

One of the issues that must be considered in interspecies comparisons of hazards from inhaled particles is inhalability of the aerosol in the atmosphere of concern. Inhalability is the fraction of suspended PM in ambient air that actually enters the nose or mouth with the volume of air inhaled and is a function of particle aerodynamic size, inspiratory flow rate, wind speed, and wind direction. Although inhalability may not be an issue for humans per se as far as exposure to ambient particles is concerned, it can be an important issue when attempting to extrapolate to humans the results of studies using animal species commonly employed in inhalation toxicological studies (Miller et al., 1995). For example, differences between rat and human become very pronounced for particles > 5 μm, and some differences are also evident for particles as small as l μm (Figure 6-10). Ménache et al. (1995) have developed equations that can be used to determine the inhalability adjustments needed as a function of particle size to compare laboratory animal and human studies.

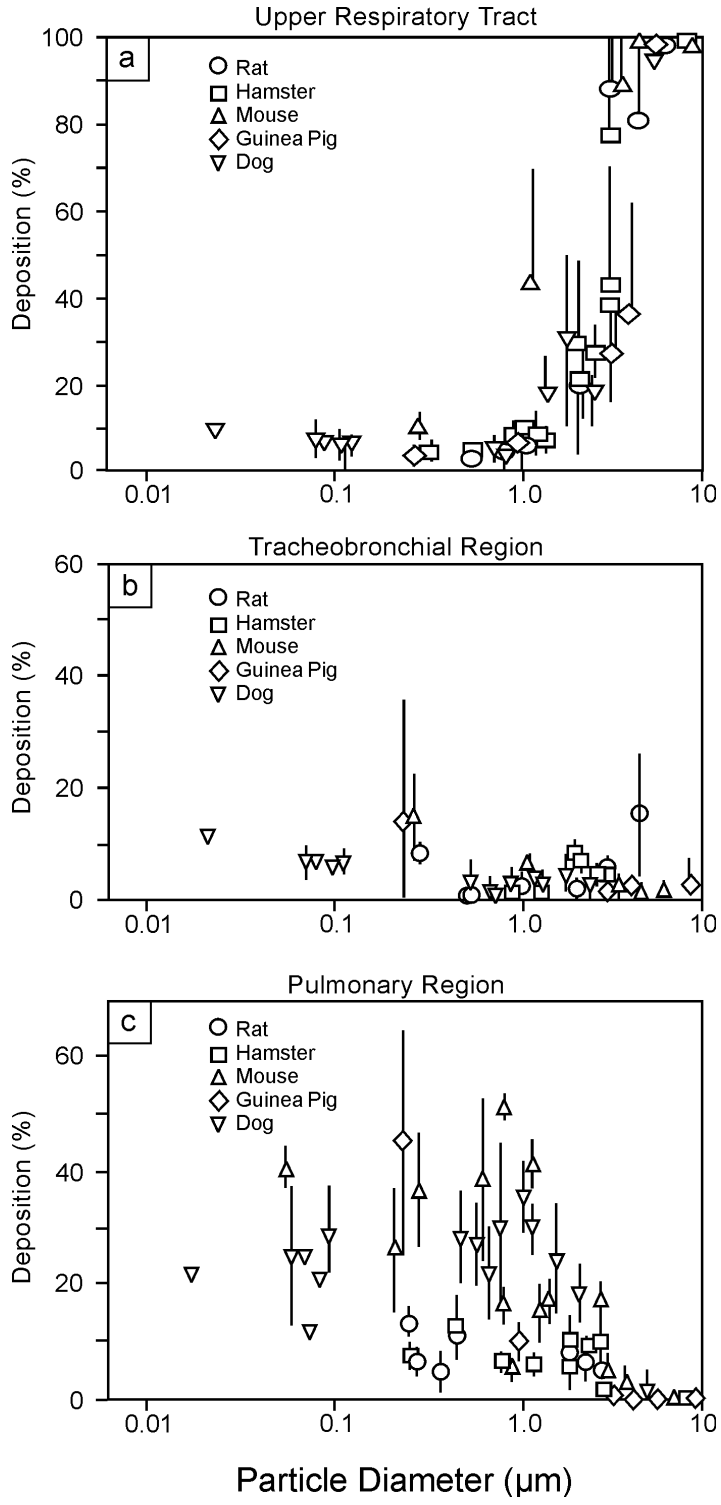

Figure 6-9. Regional deposition fraction measured in laboratory animals as a function of particle size for (a) upper respiratory tract, (b) tracheobronchial region, and (c) pulmonary region. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those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

Source: Schlesinger (1988).

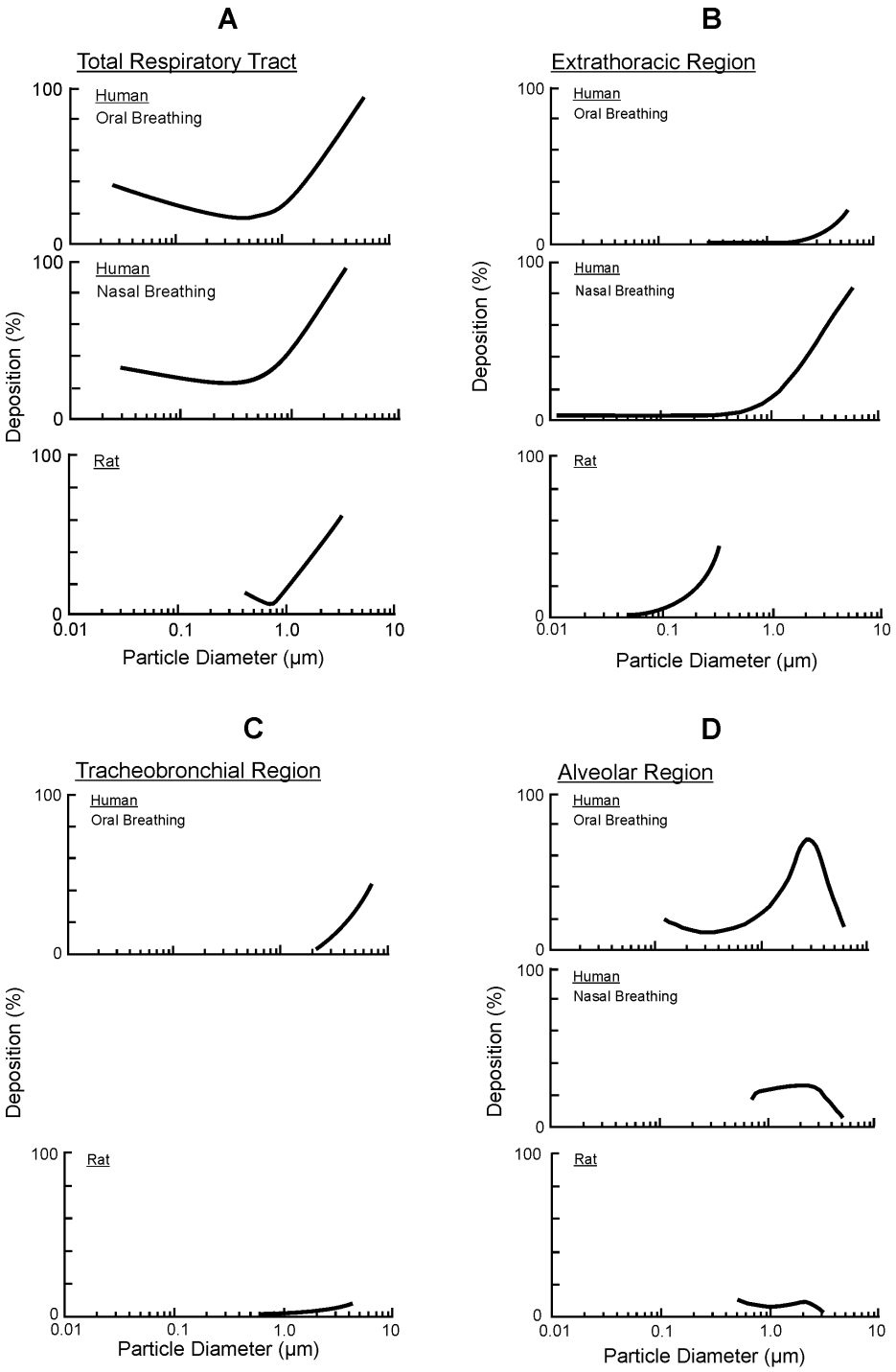

Figure 6-10. Particle deposition efficiency in rats and humans as a function of particle size for the (A) total respiratory tract, (B) thoracic region, (C) tracheobronchial region, and (D) alveolar region. Each curve represents an eye fit through mean values (or centers of ranges) for the data compiled 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).

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

Hofmann et al. (1996) attempted to account for interspecies differences in branching patterns in deposition analyses. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that morphologic asymmetry was a major determinant of the heterogeneity of local deposition patterns. They noted that many interspecies deposition calculations used morphometry that was described by deterministic lung models (i.e., the number of airways in each airway generation is constant, and all airways in a given generation have identical lengths and diameters). Such models cannot account for variability and branching asymmetry of airways in the lungs. Thus, their study employed computations that used stochastic morphometric models of human and rat lungs (Koblinger and Hofmann, 1985, 1988; Hofmann et al., 1989b) and evaluated regional and local particle deposition. Stochastic models of lung structure describe, in mathematical terms, the inherent asymmetry and variability of the airway system, including diameter, length, and angle. They are based on statistical analyses of actual morphometric analyses of lungs. The model also incorporated breathing patterns for humans and rats. In a later analysis (Hofmann and Bergmann, 1998), the dependence of deposition on particle size was found to be qualitatively similar in both rats and humans: deposition minima were found for total deposition as well as deposition within the TB and A regions in the size range of 0.1 to 1 μm. In addition, a deposition maximum occurred at about 0.02 to 0.03 μm and between 3 and 5 μm in both species.

The deposition decrease in the A region at the smallest and largest sizes resulted from the filtering efficiency of upstream airways. Although deposition patterns were qualitatively similar in rat and human, deposition in the human lung appeared to be consistently higher than in the rat in all regions of the lung (TB and A) over the entire size range. Both species showed a similar pattern of dependence of deposition on flow rate.

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, indicating fairly uniform deposition throughout the lungs. On the other hand, in the resting rat, the ratio was 2.24, indicating greater deposition in the TB region than in the A region. However, by mimicking light activity in the rat, the ratio was reduced to 0.97, similar to the human. These data underscore the need for dose-response studies and for models that are capable of adjusting for the dosimetric differences between species.

The relative distribution of particles deposited within the bronchial and alveolar regions of the airways may differ in the lungs of animals and humans for the same total amount of

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

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

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

6.3 PARTICLE CLEARANCE AND TRANSLOCATION

This section discusses the clearance and translocation of particles that have deposited in the respiratory tract. First, a basic overview of biological mechanisms and pathways of clearance in the various region of the respiratory tract is presented. This is followed by an update on regional kinetics of particle clearance. Interspecies patterns of clearance are then addressed, followed by new information on biological factors that may modulate clearance.

6.3.1 Mechanisms and Pathways of Clearance

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

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

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

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

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

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

Source: Schlesinger (1995).

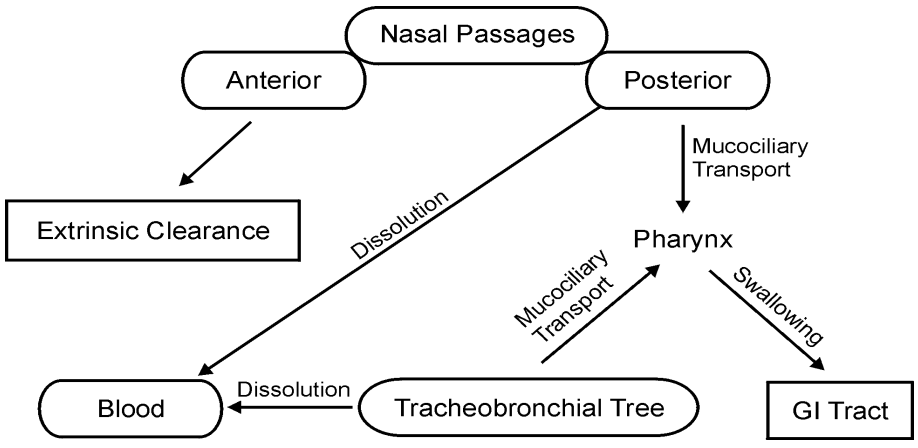

Figure 6-11. Major clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree.

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

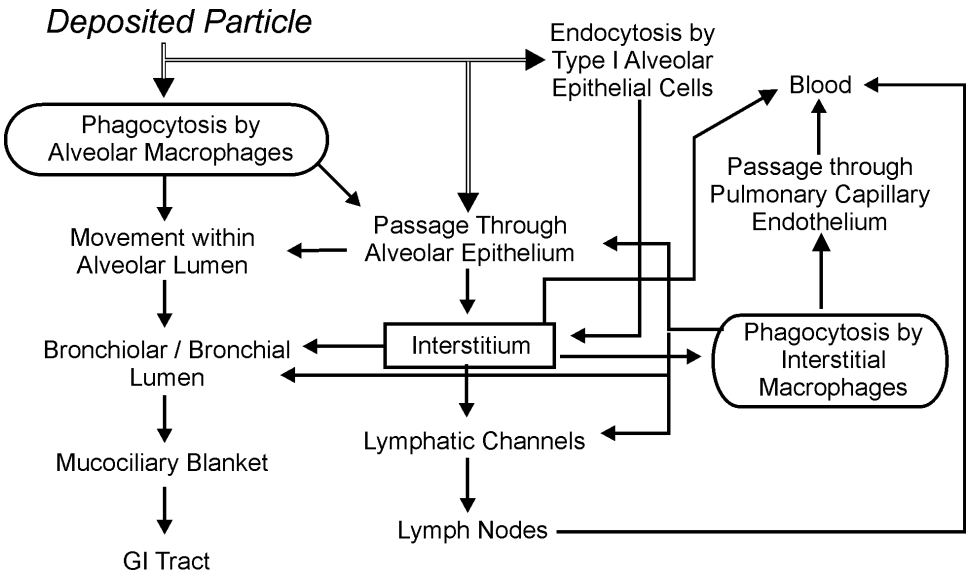

Figure 6-12. Diagram of known and suspected clearance pathways for poorly soluble particles depositing in the alveolar region. (The magnitude of various pathways may depend upon size of deposited particle.)

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

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.

6.3.1.2 Tracheobronchial Region

Poorly soluble particles deposited within the TB region are cleared by mucociliary transport towards the oropharynx, followed by swallowing. Poorly soluble particles also may traverse the epithelium by endocytotic processes, entering the peribronchial region, be engulfed via phagocytosis by airway macrophages (which can then move cephalad on the mucociliary blanket), or enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles

may be absorbed through the epithelium into the blood. It has been shown that blood flow affects translocation from the TB region in that decreased bronchial blood flow is associated with increased airway retention of soluble particles (Wagner and Foster, 2001). There is, however, evidence that even soluble particles may be cleared by mucociliary transport (Bennett and Ilowite, 1989; Matsui et al., 1998; Wagner and Foster, 2001).

6.3.1.3 Alveolar Region

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

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

Particle-laden macrophages may be cleared from the A region along a number of pathways. As noted in Figure 6-11, this includes cephalad transport via the mucociliary system after the cells reach the distal terminus of the mucus blanket; movement within the interstitium to a lymphatic channel; or perhaps traversing of the alveolar-capillary endothelium directly entering the bloodstream. Particles within the lymphatic system may be translocated to tracheobronchial lymph nodes, which can become reservoirs of retained material. Particles subsequently reaching the postnodal lymphatic circulation will enter the blood. Once in the systemic circulation, these particles or transmigrated macrophages can travel to extrapulmonary organs. Deposited particles that are not ingested by alveolar macrophages may enter the interstitium where they are subject to phagocytosis by resident interstitial macrophages, and may travel to perivenous, peribronchiolar or subpleural sites where they become trapped, increasing particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the

redistribution of initially diffuse deposits into focal aggregates. Some particles or components can bind to epithelial cell membranes, macromolecules, or to other cell components, delaying clearance from the lungs.

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

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

6.3.2 Clearance Kinetics

The kinetics of clearance have been reviewed in U.S. Environmental Protection Agency (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 particles retained longer than 24 h. Based upon asymmetric stochastic human-lung modeling-data, inter-subject variability in path length and the number of generations to the alveoli, which may result in some material reaching the alveoli even with shallow breathing, can explain the experimental observations while still fitting a single compartment clearance model. Other studies described below, however, do support the concept that TB regional clearance consists of both a fast and a slow component.

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

In a study to examine retention kinetics in the tracheobronchial tree (Falk et al., 1999), nonsmoking healthy adults inhaled radioactively tagged 6.1-μm particles at both a normal flow rate and a slow flow rate designed to deposit particles preferentially in small ciliated airways. Lung retention was measured from 24 h to 6 mo after exposure. Following normal flow rate inhalation, 14% of the particles retained at 24 h cleared with a half time of 3.7 days and 86% with a half time of 217 days. Following slow flow rate inhalation, 35% of the particles retained at 24 h cleared with a half time of 3.6 days and 65% with a half time of 170 days. Estimates using a number of mathematical models indicated higher deposition in the bronchiolar region (generations 9 through 15) with the slow rate inhalation compared to the normal rate. The experimental data and predictions of the deposition modeling indicated that 40% of the particles deposited in the conducting airways during the slow inhalation were retained after 24 h. The

particles that cleared with the shorter half time were mainly deposited in the bronchiolar region, but only about 25% of the particles deposited in this region cleared in this phase. This study provided additional confirmation for a phase of slow clearance from the bronchial tree.

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

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

6.3.2.3 Alveolar Region

Particles deposited in the A region generally are retained longer than are those deposited in airways cleared by mucociliary transport. There are limited data on alveolar clearance rates in humans. Within any species, reported clearance rates vary widely because, in part, of different properties of the particles used in the various studies. Furthermore, some chronic experimental studies have employed high concentrations of poorly soluble particles that may have interfered with normal clearance mechanisms, resulting in clearance rates different from those that would typically occur at lower exposure levels. Prolonged exposure to high particle concentrations is

associated with what is termed particle "overload." This is discussed in greater detail in Section 6.4.

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

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

Uningested particles may penetrate into the interstitium within a few hours following deposition. This transepithelial passage seems to increase as particle loading increases, especially to that level above which macrophage numbers increase (Ferin, 1977; Ferin et al., 1992; Adamson and Bowden, 1981). It also may be particle size dependent because insoluble ultrafine particles (< 0.1 μm diameter) of low intrinsic toxicity show increased access to the interstitum and greater lymphatic uptake than do larger particles of the same material (Oberdörster et al., 1992; Ferin et al., 1992). However, ultrafine particles of different materials may not enter the interstitium to the same extent. Similarly, a depression of phagocytic activity, a reduction in macrophage ability to migrate to sites of deposition (Madl et al., 1998), or the deposition of large numbers of ultrafine particles may increase the number of free particles in the alveoli, perhaps enhancing removal by other routes. In any case, free particles may reach the lymph nodes perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985) although this route is not definitive and may be species dependent.

Kreyling et al. (2002) studied the translocation of insoluble ultrafine ^{192}Ir radiolabeled particles (15 and 80 nm count median diameter) inhaled by healthy, young adult, male rats

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

The extent of lymphatic uptake of particles may depend on the effectiveness of other clearance pathways in that lymphatic translocation likely increases when the phagocytic activity of alveolar macrophages decreases. This may be a factor in lung overload. However, it seems that the deposited mass or number of particles must exceed some threshold below which increases in loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle and Brieger, 1961). In addition, the rate of translocation to the lymphatic system may be somewhat particle-size dependent. Although no human data are available, translocation of latex particles to the lymph nodes of rats was greater for 0.5- to 2-µm particles than for 5- and 9-µm particles (Takahashi et al., 1992), and particles within the 3- to 15-µm size range were found to be translocated at faster rates than were larger sizes (Snipes and Clem, 1981). On the other hand, translocation to the lymph nodes was similar for both 0.4-µm barium sulfate or 0.02-µm gold colloid particles (Takahashi et al., 1987). It seems that particles $\leq$ 2 µm clear to the lymphatic system at a rate independent of size; and it is particles of this size, rather than those $\geq$ 5 µm, that would have significant deposition within the A region following inhalation. In any case, the normal rate of translocation to the lymphatic system is quite slow; and

elimination from the lymph nodes is even slower, with half times estimated in tens of years (Roy, 1989).

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

As indicated in both the toxicology and epidemiology chapters of this document (Chapters 7 and 8), there is concern about how ambient PM affects the cardiovascular system. Thus, an important dosimetric issue involves the pathways by which inhaled and deposited particles in the lungs could affect extrapulmonary systems. Pathways by which PM, constituents of PM, or cytokines released by the respiratory tract in response to PM could affect systems distal to the respiratory tract occur have been recently described. Nemmar et al. (2001) instilled hamsters with radioactively-labeled colloidal albumin particles (diameter $\leq$ 0.080 μm) as a model for ambient ultrafine particles and measured the label appearing in systemic blood and various extrapulmonary organs up to 1 h postexposure. They found label in blood within 5 minutes after instillation. In their subsequent studies in which healthy volunteers were challenged with inhalation of ^{99m}Technitum-labeled ultrafine (< 100 nm) carbon particles (Nemmar et al., 2002), the radioactivity was detected in blood as early as 1 min, reaching a maximum between 10 and 20 min after inhalation of the aerosol. While label was also noted in the other extrapulmonary organs examined (namely liver, heart, spleen, kidneys, and brain), the liver had the highest levels and these increased with increasing time postexposure while the second highest levels were noted in the heart or kidney, depending upon the instilled concentration. This suggests that ultrafine particles can rapidly diffuse from the lungs into the systemic circulation, thus providing a pathway by which ambient PM may rapidly affect extrapulmonary organs.

In another study, Takenaka et al. (2001) exposed rats by inhalation to 0.015 μm particles of elemental silver and found elevated levels of silver (Ag) in various extrapulmonary organs up to 7 days postexposure. They found that the amount of Ag in the lungs decreased rapidly with time, and, by day 7, only about 4% of the initial lung burden remained. At day 0, Ag was already found in the blood. By 1 day postexposure, Ag had been distributed to the liver, kidney, heart, and brain. The Ag concentration was highest in the kidney, followed by the liver, and then the heart. This study also indicates that inhaled ultrafine particles were rapidly cleared from the lungs. A similar clearance pattern was found after intratracheal instillation of $AgNO_3$ solution. Therefore, the investigators postulated that the rapid clearance of elemental silver particles was due to a fast dissolution of ultrafine silver particles into the lung fluid and subsequent diffusion into the blood stream although a possibility of direct translocation of solid particles into the blood stream was not excluded. The investigators also instilled an aqueous suspension of elemental silver particles (100+ μm) into some animals; in this case, there was more retention in the lungs, which was ascribed to phagocytic accumulation of agglomerated particles in alveolar macrophages and slow dissolution of particles in cells. Thus, this study also suggested that particle size and the tendency of particles to aggregate can affect the translocation pathway from the lungs. Earlier studies (Huchon et al., 1987; Peterson et al., 1989; Morrison et al., 1998) investigated lung clearance of labeled macromolecule solutes with widely varying molecular weight and labeled albumin as well as albumin ultrafine aggregates. Clearance rates found from these earlier studies were much slower than recent studies described above, suggesting that the possibility of a fast clearing 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 toxicological assessment necessitates that clearance kinetics in such animals be related to those in humans. The basic mechanisms and overall patterns of clearance from the respiratory tract are similar in humans and most other mammals. However, regional clearance rates can show substantial variation between species, even for similar particles deposited under comparable exposure conditions, as extensively reviewed elsewhere (U.S. Environmental Protection Agency, 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 were retained persistently after uptake by macrophages (Snipes and Clem, 1981; Oberdörster et al., 1992). The ultimate implication of interspecies differences in clearance that need to be considered in assessing particle dosimetry is that the retention of deposited particles can differ between species and may result in differences in response to similar PM exposure atmospheres.

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

6.3.4 Factors Modulating Clearance

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

6.3.4.1 Age

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

6.3.4.2 Gender

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

6.3.4.3 Physical Activity

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

6.3.4.4 Respiratory Tract Disease

Various respiratory tract diseases are associated with clearance alterations. Evaluation of clearance in individuals with lung disease requires careful interpretation of results because

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

In another study, Svartengren et al. (1996b) examined clearance from the TB region in adults with chronic bronchitis who inhaled 6-μm Teflon particles. Based on calculations, particle deposition was assumed to be in small ciliated airways at low flow and in larger airways at higher flow. The results were compared to those obtained in healthy subjects from other studies. At low flow, a larger fraction of particles was retained over 72 h in people with chronic bronchitis compared to healthy subjects, indicating that clearance resulting from spontaneous cough could not fully compensate for impaired mucociliary transport in small airways. For larger airways, patients with chronic bronchitis cleared a larger fraction of the deposited particles over 72 h than did healthy subjects, but this was reportedly because of differences in deposition resulting from airway obstruction.

An important mechanism of clearance from the tracheobronchial region, under some circumstances, is cough. Although cough can be a reaction to an inhaled stimulus, in most individuals with respiratory infections and disease, spontaneous coughing also serves to clear the upper bronchial airways by dislodging mucus from the airway surface. Recent studies confirm that this mechanism likely plays a significant role in clearance for people with mucus hypersecretion, at least for the upper bronchial tree, and for a wide range of deposited particle sizes (0.5 to 5 μm; Toms et al., 1997; Groth et al., 1997). There appears to be a general trend towards an association between the extent (i.e., number) of spontaneous coughs and the rate of particle clearance; faster clearance is associated with a greater number of coughs (Groth et al., 1997). Thus, recent evidence continues to support cough as an adjunct to mucociliary movement in the removal of particles from the lungs of individuals with COPD. However, some recent

evidence suggests that, like mucociliary function, cough-induced clearance may become depressed with worsening airway disease. Noone et al. (1999) found that the efficacy of clearance via cough in patients with primary ciliary dyskinesia (who rely on coughing for clearance because of immotile cilia) correlated with lung function (FEV_1), in that decreased cough clearance was associated with decreased percentage of predicted FEV_1.

Earlier 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 or cigarette smoke. Earlier studies performed with particle instillation showed that alveolar epithelial damage in mice at the time of deposition resulted in increased translocation of inert carbon to pulmonary interstitial macrophages (Adamson and Hedgecock, 1995). A similar response was observed in a more recent assessment (Adamson and Prieditis, 1998), 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 with normal clearance mechanisms and produced clearance rates different from those that would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with a phenomenon that has been termed particle "overload," defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate that exceeds the capacity of that clearance pathway. It has been suggested that, in the rat, overload is more dependent upon the volume rather than the mass of particles (Tran et al., 2000) and that volumetric

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The most important factor that produces high surface deposition doses of inhaled particles in the TB region is the disturbed airflow produced by airway bifurcations. An enhanced deposition of particles (for all sizes that have been examined) is seen at bifurcations in the TB tree (Balashazy et al., 1999; Bell and Friedlander, 1973; Kaye et al., 2000; Oldham et al., 2000; Schlesinger et al., 1982). The dose enhancement factor is dependent on both inhaled particle diameter and the size of the deposition region under consideration. Using the computational fluid dynamic modeling in a physiologically realistic (human TB tree) 3-dimensional group of bifurcations, Balashazy et al. (1999) provided numerical enhancement (over average airway surface deposition doses) factors. For the smallest region considered, which would comprise less than a few hundred epithelial cells, the enhancement factors ranged from 52-fold for 0.01 μm diameter particles up to 113-fold for 10 μm diameter particles. An enhancement factor of

81-fold was calculated for 1 μm diameter particles. Thus, for the purposes of simulating the exposure of the heavily dosed TB bifurcation cells to $PM_{10}/PM_{2.5}$, an enhancement factor of 80-fold is reasonable. Taken together, the combined dose enhancing effects of increased ventilation (2-fold), oral breathing (2-fold), lung disease (2-fold) and bifurcation effects (80-fold), one could expect populations of epithelial cells to experience enhanced deposition (over average surface deposition) of about 640-fold. Considering that clearance impairment may also be a factor in subpopulations with some disease states, the buildup of particles at such TB bifurcations further increases the dose in relation to healthy individuals.

As a final consideration in this susceptibility scenario, the proximity of exposure to sources of PM may be important. Although data are sparse in this regard, Zhu et al. (2002) have measured time-averaged concentrations of black carbon and particle number at various distances downwind from freeways in Los Angeles. In comparison to upwind concentrations, concentrations at 30m downwind were about 4-fold higher for black carbon, and about 3-fold higher for particle number. A factor of 3 for increased dose over the average might be expected for this subpopulation. By taking all of the above factors into account, it is not unreasonable to expect local PM doses to groups of cells in potentially susceptible subpopulations to be 3-4,000 times greater than the average TB surface exposures for the general population. Other scenarios could be evaluated that lead to greater, or lesser, local dose estimates.

An estimate of the average surface deposition dose in the TB tree of a individual (with COPD) exposed to $PM_{2.5}$ for 24 hours at the current 24 hour NAAQS (65 $\mu g/m^3$) can be calculated using the NCRP (1997) report and values for the surface area of the TB region in adults. Assuming 5% of the inhaled particles deposit on a TB surface of 2,470 cm^2 (Mercer et al., 1994), and that no clearance occurs, the average surface deposition would be about 0.02 $\mu g/cm^2$ of epithelium. Applying an enhancement factor of 3,000 to represent the most heavily exposed epithelial cells yields a surface deposition of 57 $\mu g/cm^2$. Assuming a rat has a TB surface area of 27.2 cm^2 (Mercer et al., 1994) and that the instillation of a PM suspension exposes 10% of this area (Pritchard et al., 1985), an instillation of 150 μg could be reasonable. It should be noted that even greater delivered doses to respiratory tract cells would be expected in less well developed regions of the world with significantly higher levels of particulate air pollutants.

In conclusion, well-conducted instillation studies are valuable for examining the relative toxicity of particulate materials and for providing mechanistic information that is useful for interpreting in vitro and inhalation studies. However, because mechanisms of injury may vary with the delivered dose, it would be useful if instillation studies designed to provide information relevant to human risk assessment were accompanied by dosimetric calculations.

6.6 MODELING THE DISPOSITION OF PARTICLES IN THE RESPIRATORY TRACT

6.6.1 Modeling Deposition, Clearance, and Retention

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

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

Recent reports involve modeling the deposition of ultrafine particles and deposition at airway bifurcations. Zhang and Martonen (1997) used a mathematical model to simulate diffusion deposition of ultrafine particles in the human upper tracheobronchial tree and compared the results to those in a hollow cast obtained by Cohen et al. (1990). The model results were in good agreement with experimental data. Zhang and Martonen (1997) studied the

inertial deposition of particles in symmetric three-dimensional models of airway bifurcations, mathematically examining effects of geometry and flow. They developed equations for use in predicting deposition based on Stokes numbers, Reynolds numbers (a dimensionless number that describes the tendency for a flowing fluid to change from laminar flow to turbulent flow), and bifurcation angles for specific inflows.

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

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

Musante and Martonen (2000c) developed an age-dependent theoretical model to predict dosimetry in the lungs of children. The model includes the dimensions of individual airways and

the geometry of branching airway networks within developing lungs and breathing parameters as a function of age. The model suggests that particle size, age, and activity level markedly affect deposition patterns of inhaled particles. Simulations thus far predict a lung deposition fraction of 38% in an adult and 73% (nearly twice as high) in a 7-mo-old for 2-µm particles inhaled during heavy breathing. The authors conclude that this model will be useful for estimating dose delivered to sensitive subpopulations such as children.

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

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

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

predictions and experimental data depending on the flow profiles used, indicating that use of more realistic parameters is essential to improving the accuracy of model predictions.

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

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

Another respiratory tract dosimetry model was developed concurrently with the ICRP model by the National Council on Radiation Protection and Measurements (NCRP, 1997).

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

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

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

respiratory tract. The rates of dissolution-absorption of particles and their constituents were derived from clearance data primarily from laboratory animals. The effect of body growth on particle deposition also was considered in the model, but particle clearance rates were assumed to be independent of age. Some consideration for compromised individuals was incorporated into the model by altering normal rates for the NOPL and TB regions.

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

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

It is important to evaluate these accumulation patterns, especially when assessing ambient chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined as "species-dependent concentrations of airborne particles which, when chronically inhaled, produce equal lung deposits of inhaled particles per gram of lung during a specified exposure period" (Schlesinger et al., 1997). Available data and approaches with which to evaluate exposure atmospheres that produce similar respiratory tract burdens in laboratory animals and humans were discussed in detail in the 1996 PM AQCD.

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

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

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

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

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

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

6.6.2 Models To Estimate Retained Dose

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

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

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

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

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

Additional research must be done to provide the information needed to evaluate properly retention of particles in conducting airways. However, a number of earlier studies, discussed in the 1996 document and in Section 6.2.2.2 herein, noted that some particles were retained for

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

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

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

Dosimetric models may be used to adjust for differences in the exposure-dose relationship in different species, thus allowing for comparison of lung responses at different doses. In a series of papers Kuempel (Kuempel 2000, 2001a; Kuempel 2001b) presents a biologically based

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

6.6.3 Fluid Dynamics Models for Deposition Calculations

The available models developed to simulate particulate matter deposition in the lung are based on simplifying assumptions about the morphometry of the lung and the fluid dynamics of inspired air through a branching airway system. As new models are developed, they will better predict particle deposition patterns in a more realistic airway geometry under realistic flow conditions that can result in local 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 indicated that the results of the model compared favorably with experimental data and that the model will be incorporated into a particle deposition model which will allow for the evaluation of the nonuniformity of deposition within the lungs resulting from the physiological situation of nonuniform distribution of ventilation. Computational fluid dynamics (CFD) modeling adds another step to better model development by providing increased ability to predict local airflow and particle deposition patterns and 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 flow streams after solving for the particles' equation of motion. Such CFD models have been developed for different regions of the respiratory tract, including the nasal cavity (Yu et al., 1998; Sarangapani and Wexler, 2000); larynx (Martonen et al. 1993; Katz et al., 1997; Katz, 2001); major airway bifurcations (Gradon and Orlicki, 1990; Balásházy and Hofmann, 1993a,b, 1995, 2001; Heistracher and Hofmann, 1995; Lee et al., 1996; Zhang et al., 1997, 2000, 2001, 2002; Comer et al., 2000, 2001a,b); and alveoli (Tsuda et al., 1994a,b; Darquenne, 2001).

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

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

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

Stapleton et al. (2000) investigated deposition of a polydisperse aerosol (MMD = 4.8 μm and GSD = 1.65) in a replica of a human mouth and throat using both experimental results and 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.

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

Gradon and Orlicki (1990) computed the local deposition flux of submicron size particles in a three-dimensional bifurcation model for both inhalation and exhalation, and they found enhanced deposition in the carinal ridge region during inspiration and in the central zone of the parent airway during expiration. Numerical models of particle deposition in symmetric three-dimensional bifurcations were developed by Balásházy and Hofmann (1993a,b), and these were

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

Zhang et al. (1997) numerically simulated particle deposition in three-dimensional bifurcating airways (having varying bifurcation angles) due to inertial impaction during inspiration for a wide range of Reynolds numbers (100-1000). Inlet velocity profile, flow Reynolds number, and bifurcation angle had a substantial effect on particle deposition efficiency. Based on the simulated results, equations were derived for particle deposition efficiency as a function of nondimensional parameters, such as Stokes number, Reynolds number, and bifurcation angle, and were shown to compare favorably with available experimental results. More recently, Comer et al. (2000) have estimated the deposition efficiency of 3-, 5-, and 7-μm particles in a three-dimensional double bifurcating airway model for both in-plane and out-of-plane configurations for a wide range of Reynolds numbers (500-2000). They demonstrated deposition in the first bifurcation to be higher than in the second bifurcation, with deposition mostly concentrated near the carinal region. The non-uniform flow generated by the first bifurcation had a dramatic effect on the deposition pattern in the second bifurcation. Based on these results, they concluded that use of single bifurcation models is

inadequate to capture the complex fluid-particle interactions that occur in multigeneration airway systems.

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

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

Most CFD models use constant inspiratory or expiratory flows for simplicity and practical reasons. However, the respiratory airflow is cyclic, and such flow characteristics cannot be fully described by constant flows. Recent studies of Zhang et al. (2002) investigated particle deposition in a triple bifurcation airway model under cyclic flow conditions mimicking resting and light activity breathing. Deposition dose was obtained for every mm square area. They found that deposition patterns were similar to those obtained with constant flows. However, deposition efficiencies were greater with the cyclic flows than constant flows, and the difference could be as high as 50% for $0.02 < \text{mean Stk} < 0.12$ during normal breathing. The CFD results are qualitatively comparable to experimental data (Kim and Garcia, 1991) that showed about

25% increase in deposition with cyclic flows. With further improvement of airway morphology and computational scheme, CFD modeling could be a valuable tool for exploring the microdosimetry in the airway structure.

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

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

6.6.4 Modeling Results Obtained with Models Available to the Public

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

6.6.4.1 International Commission on Radiological Protection (ICRP)

The LUDEP (Lung Dose Evaluation Program; National Radiologic Protection Board, 1994) model was developed concurrently with the ICRP (International Commission on Radiological Protection, 1994) respiratory tract model mainly to help the ICRP Task Group examine the model in detail by testing the predictions of deposition, clearance and retention of

inhaled radionuclides against experimental data, and by determining the model's implications for doses to the respiratory tract (ICRP, 1994; NRPB, 1994). This model was designed to represent the deposition of inhaled particles in the respiratory tract, the subsequent biokinetic behavior of inhaled radionuclides, and the doses delivered to the respiratory tract. Although created for calculating the internal dose of radionuclides, the model is useful for determining the deposition of nonradioactive materials, but not for describing clearance of nonradioactive particles.
In particular, the model has wide applicability for calculating the regional deposition of particles in the respiratory tract based on particle size, body size (age), breathing rate, activity patterns, and exposure environment. The overall dosimetric model for the respiratory tract consists of several critical elements important for dose calculations including detailed descriptions of morphometry, respiratory physiology, and deposition. The morphometric element of the model describes the structure of the respiratory tract and its dimensions. A description of respiratory physiology provides the rates and volumes of inhaled and exhaled air which determines the amount of material that can be deposited in the respiratory tract. Deposition characterizes the initial distribution of the inhaled material within the different regions of the respiratory tract specific to the age and gender of the subject and the physiological parameters. The ICRP model covers the particle size range from 0.001 to 100 μm.

Two simulations were run to demonstrate some aspects of deposition as predicted by the ICRP model. Respiratory parameters for a worker with a moderately high activity level and a young adult with a lower activity level are given in Table 6-3. Each simulation was run for nasal breathing and mouth breathing. The ICRP model calculates deposition in five compartments:

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

In the presentation of the model results, ET1 and ET2 are combined to give an ET (extrathoracic region), BP and bb are combined to give a TB (tracheobronchial) region, and Al gives the A

TABLE 6-3. RESPIRATORY PARAMETERS USED IN LUDEP MODEL

Activity	Percent	Ventilation Rate (m^3/hr)	Activity Related Physiological Parameters: Frequency (breaths/min)	Activity Related Physiological Parameters: Tidal Volume (mL)
Adult Male ICRP Defaults for Environmental Outdoor Exposure				
Sleep	0	0.45	12	625
Sitting	50	0.54	12	750
Light Exercise	38	1.5	20	1250
Heavy Exercise	12	3	26	1923
Mean		1.2		
Young Adult				
Sitting	100	.45	15	500

(alveolar) region. Results are shown in Figures 6-13 to 6-15. Figure 6-13 shows the total and regional deposition as a function of particle size for the worker: nasal breathing (13a), mouth breathing (13b), and a comparison of nasal and mouth breathing for the TB and A regions (13c). Figure 6-14 gives similar results for the young adult. For both simulations, the deposition is a minimum between 0.1 and 1 μm diameter (the accumulation mode size range) and increases for larger (coarse mode) and smaller (ultrafine particle) size ranges. For ultrafine particles, TB deposition peaks between 0.001 and 0.01 μm and A deposition peaks between 0.01 and 0.1 μm.

The comparisons of nasal and mouth breathing in Figures 6-13c and 6-14c show almost no difference in deposition between 0.01 and 1 μm. Below 0.1 more particles are removed by diffusion in the extrathoracic (ET) region while above 1.0 more particles are removed by impaction in the ET region. Therefore, mouth breathing leads to greater deposition of coarse mode particles ($D_a > 1$ μm) and of the smaller ultrafine particles ($D_p < 0.01$ μm). The A deposition approaches zero as particle size increases to 10 μm. However, TB deposition continues for larger particle sizes.

The TB and A deposition patterns of the worker under moderate activity and the young adult under low activity are compared in Figure 6-15a and b. Increased activity lowers the

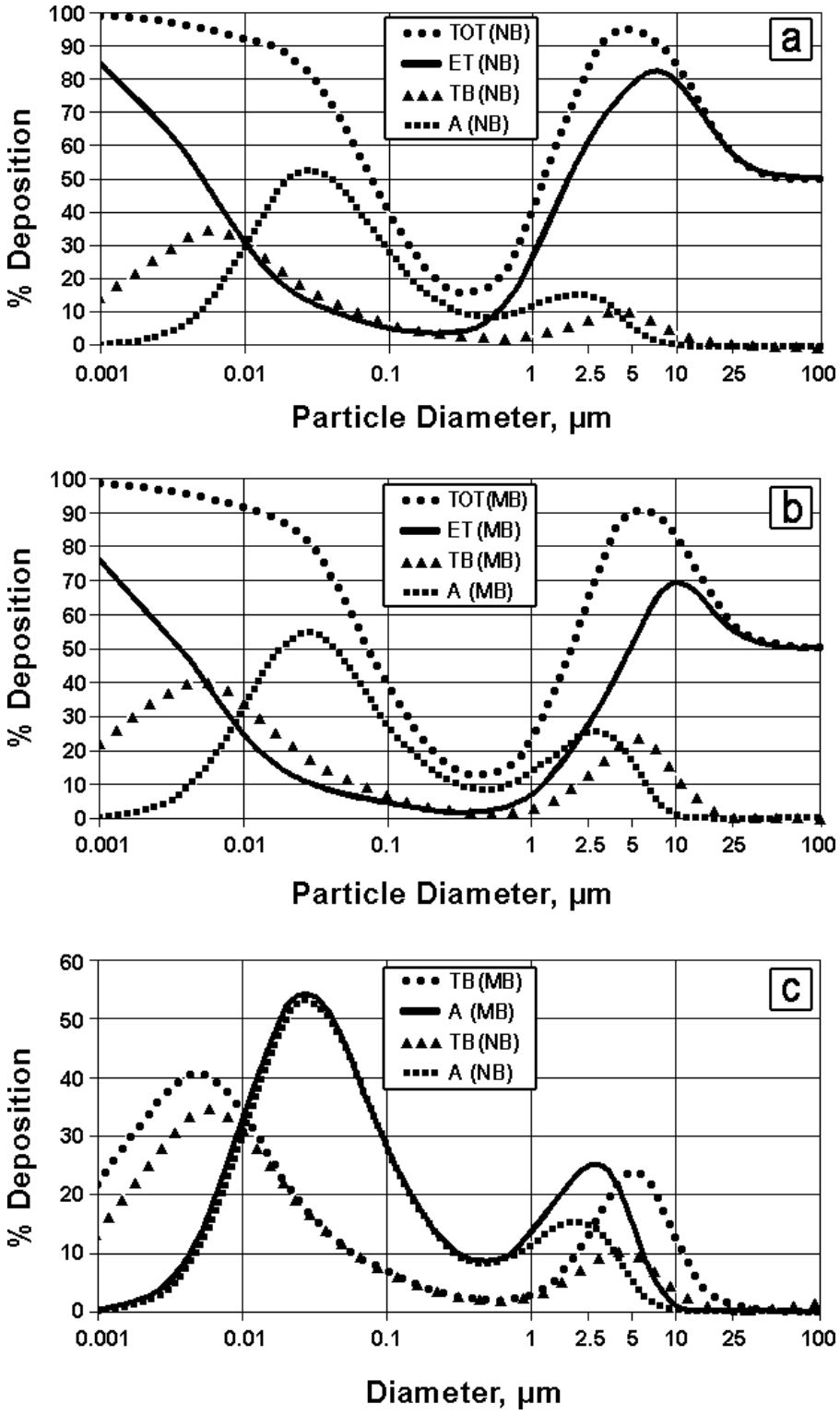

Figure 6-13. Percent deposition for total results of LUDEP model for an adult male worker (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions. Respiratory parameters given in Table 6-3. (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison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

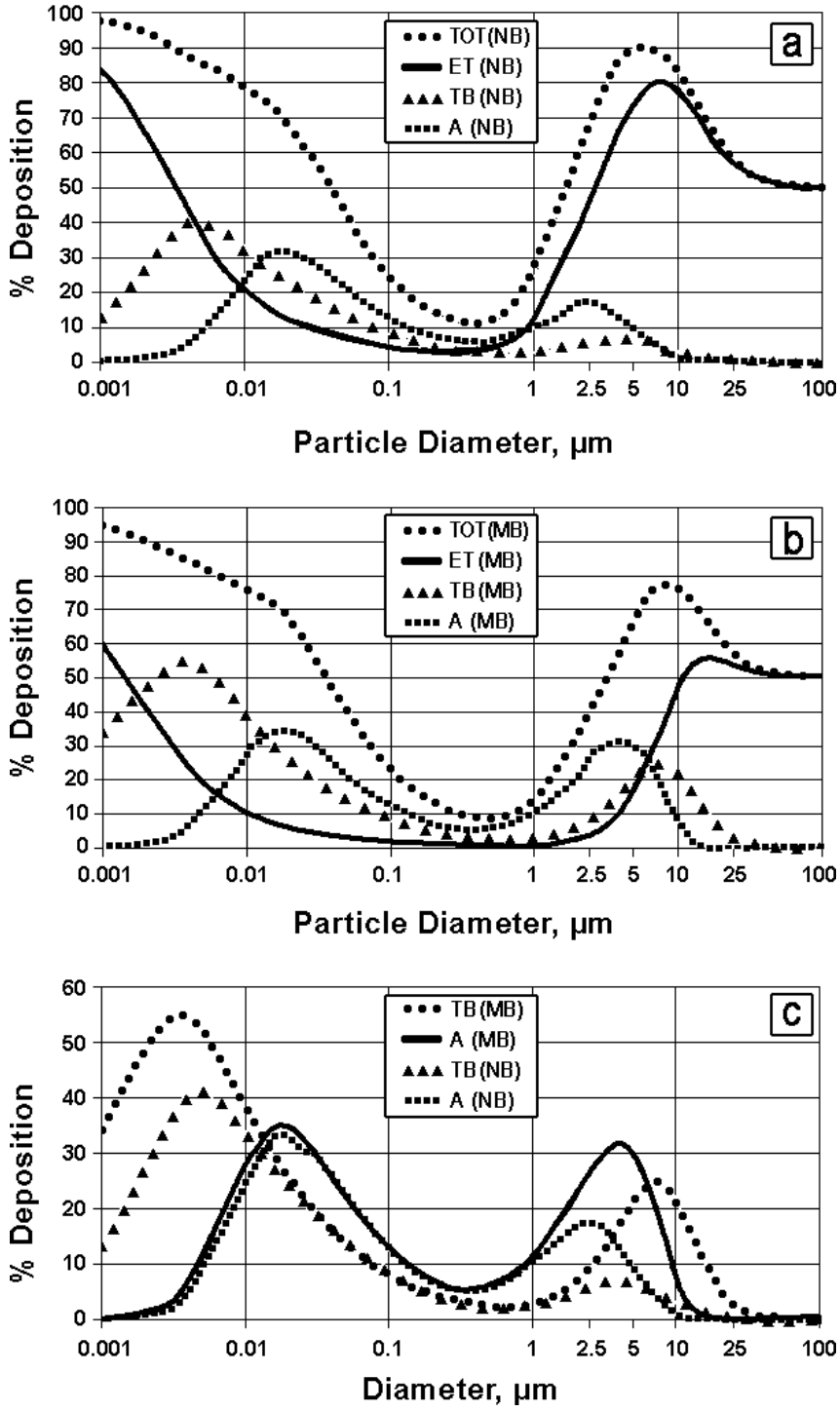

Figure 6-14. Percent deposition for total results of LUDEP model for a young adult (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions. Respiratory parameters given in Table 6-3. (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison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

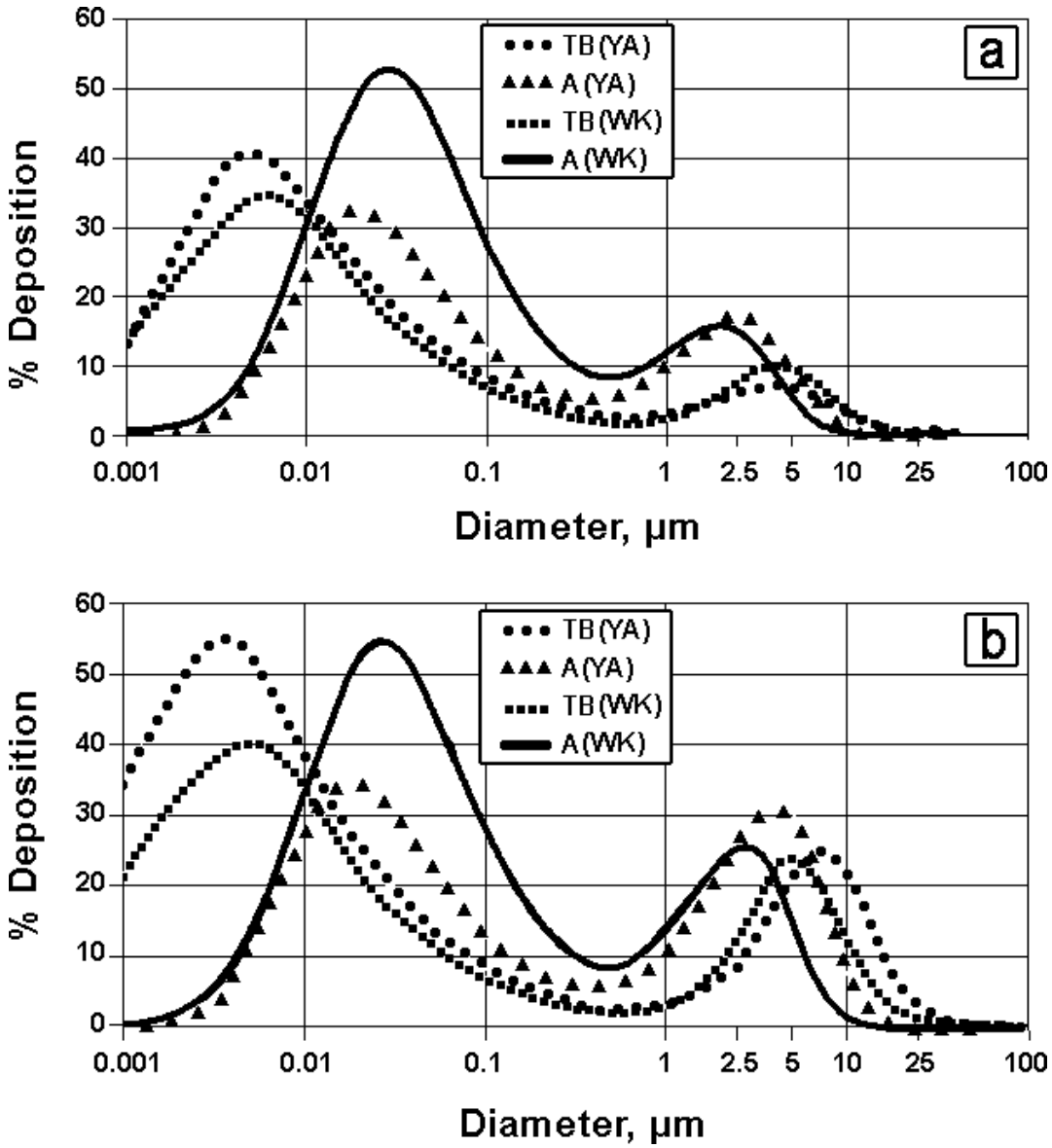

Figure 6-15. Comparison of percent deposition in the TB and A regions for a worker (WK; light exercise) and a young adult (YA; resting). (a) nasal breathing and (b) mouth breathing.

A deposition of coarse particles for nasal breathing and lowers both A and TB deposition of coarse particles for mouth breathing. It also shifts the maximum deposition for coarse particles to smaller sizes. Increased activity increases A deposition of ultrafine particles and shifts the maximum deposition to larger sizes. Increased activity also increases the A deposition of accumulation-mode particles.

6.6.4.2 Multiple Path Particle Dosimetry Model (MPPD)

Some results from this model, developed by CIIT (the Chemical Industry Institute of Technology, USA) and RIVM (Directorate-General for Environmental Protection, The Netherlands), will be taken from a RIVM report (Winter-Sorkina and Cassee, 2002). The MPPD model allows calculation of PM deposition fractions and exposure doses for humans and rats, and includes age-specific human lung models. The MPPD model covers the particle size range from 0.01 to 10 μm. The model may be used to improve understanding of the exposure-dose-response relationships observed in environmental epidemiological studies and for extrapolation of studies in experimental animals to humans. In addition, factors resulting in increased susceptibility can be studied. The report describes the results of monodisperse aerosol deposition calculations with the MPPD model and its sensitivity to various parameters. Deposition of inhaled PM depends primarily on exposure concentrations, physical characteristics of the particles, lung morphometry, and breathing parameters, and cannot easily be measured. Therefore, computer models such as the MPPD model have proven to be important tools to analyze PM dosimetry. Because these models use an explicit set of equations which describe real-life processes, either empirically or based on first principles, they are especially suited to analyze effects of scenarios such as particulate exposure control strategies. The age of the subject, the functional capacity of the lungs, and breathing parameters as well as the individual lung morphometry are factors that significantly affect the particle deposition and can explain the susceptibility of subpopulations. Results depicting deposition as a function of minute ventilation (a surrogate for exertion or exercise level) and as a function of age by particle size for various respiratory tract regions will be shown.

6.6.4.2.1 Deposition as a function of physical exertion

Earlier studies indicate that PM deposition depends on the level of physical exertion. Information on this dependency as well as on activity patterns is necessary for an estimate of the actual exposure of a whole population. Winter-Sorkina and Cassee (2002) used the MPPD model with Yeh-Schum 5-lobe limited multiple-pass particle deposition to calculate aerosol deposition in the human adult at different levels of physical exertion. The model uses data made available by Yeh and Schum (1980) that characterizes individual airways at the level of the

segmental bronchi, but describes the airways within each lobe in a single-path manner. A separate symmetric tree represents each of the five lobes.

Levels of physical exertion for adults, corresponding representative activities and corresponding minute ventilation (CARB, 1987) used in the calculation are presented in Table 6-4. The breathing frequency and tidal volume for different physical exertion levels (Table 6-4) are calculated from minute ventilation keeping the ratio of breathing frequency and tidal volume nearly constant. For normal augmenters, the switch to oronasal breathing (combined nose and mouth breathing) is considered to occur at a minute ventilation of 35.3 L/min. Partitions of airflow between the nose and mouth as given by Niinimaa et al. (1981) are used for the oronasal breathing. The partitioning flow is assumed to be the same for inhaled and exhaled air. For minute ventilation lower than this value, breathing is only through the nose, therefore, the calculations present a discontinuity at this point. Calculations are performed for monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 μm to 10 μm and with a particle density of 1 g/cm^3. The deposited mass rates were calculated for an aerosol concentration of 140 $\mu g/m^3$.

Results on aerosol deposition as a function of physical exertion for different particle sizes are shown in Figure 6-16. The head deposition fractions for 1.3 μm, 2.5 μm and 5 μm particles increase from rest to light exercise. They decrease with a factor of respectively 2.3, 1.8, and 1.5 and further stay about constant when breathing is changed from nasal to oronasal at modest and heavy exercise with minute ventilation of 40 L/min and higher. The head deposition fraction of ultrafine particles decreases slightly from rest to light exercise. Tracheobronchial deposition fractions for ultrafine particles of 0.01 μm, 0.02 μm, and 0.04 μm decrease from rest to light exercise, decrease slightly further to heavy exercise for 0.01 μm particles and stay constant for 0.04 μm particles.

Tracheobronchial deposition fraction for coarse particles decreases slightly from rest to light exercise and rises when breathing is changed from nasal to oronasal. It increases from modest to heavy exercise especially for 5 μm particles. Tracheobronchial deposition fraction of ultrafine particles is larger than deposition fraction of coarse particles at rest, light and modest exercise, however, at heavy exercise the deposition fraction of 5 μm particles is larger than that of ultrafine particles. Pulmonary or alveolar deposition fraction of ultrafine particles increases from rest to light exercise, deposition fraction of coarse 2.5 μm and 5 μm particles decreases from rest to light exercise, rises when breathing is changed from nasal to oronasal and decreases slightly from modest to heavy exercise. Thoracic deposition fraction shows a light increase for 0.01 μm and 0.02 μm particles and a decrease for 2.5 μm and 5 μm particles from rest to light

TABLE 6-4. LEVELS OF PHYSICAL EXERTION FOR ADULT, CORRESPONDING REPRESENTATIVE ACTIVITIES, AND BREATHING PARAMETERS

Minute ventilation, L/min	Breathing frequency, min^{-1}	Tidal Volume, mL	Exertion Level	Representative activity
5	10	500	Rest	Sleep
7.5	12	625	Rest	Awake
13	16	813	Light	Walk (4 km/h); washing clothes
19	19	1,000	Light	Walk (5 km/h); bowling; scrubbing floors
25	22	1,136	Light	Dance; push a l5 kg wheelbarrow; building activities; piling firewood; walk (7 km/h)
30	24	1,250	Modest	Quiet cycling; pushing a 75 kg wheelbarrow; using a sledgehammer
35	26	1,346	Modest	Climb 3 stairs; play tennis; digging soil
40	28	1,429	Modest	Cycle (23 km/h); walk in snow; digging a trench; jogging
59 (55-63)	34	1,735	Heavy	Skiing cross-country; mountaineering; climbing stairs with weight
72	37	1,946	Very heavy	Squash and handball; chopping wood
85	40	2,125	Very heavy	Running (18 km/h); cycle racing
100 (> 100)	44	2,273	Extremely heavy	Marathon; triathlon; cross-country ski race

Source: CARB (1987).

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

6.1.4.2.2 Deposition as a function of age

An important issue in risk assessment is the age dependency of PM deposition, especially for children. The CIIT/RIVM particle deposition model includes age-specific lung models. Winter-Sorkina and Cassee (2002) used CIIT/RIVM particle deposition mode to calculate age dependent deposition for the ages and respiratory parameters given in Table 6-5.

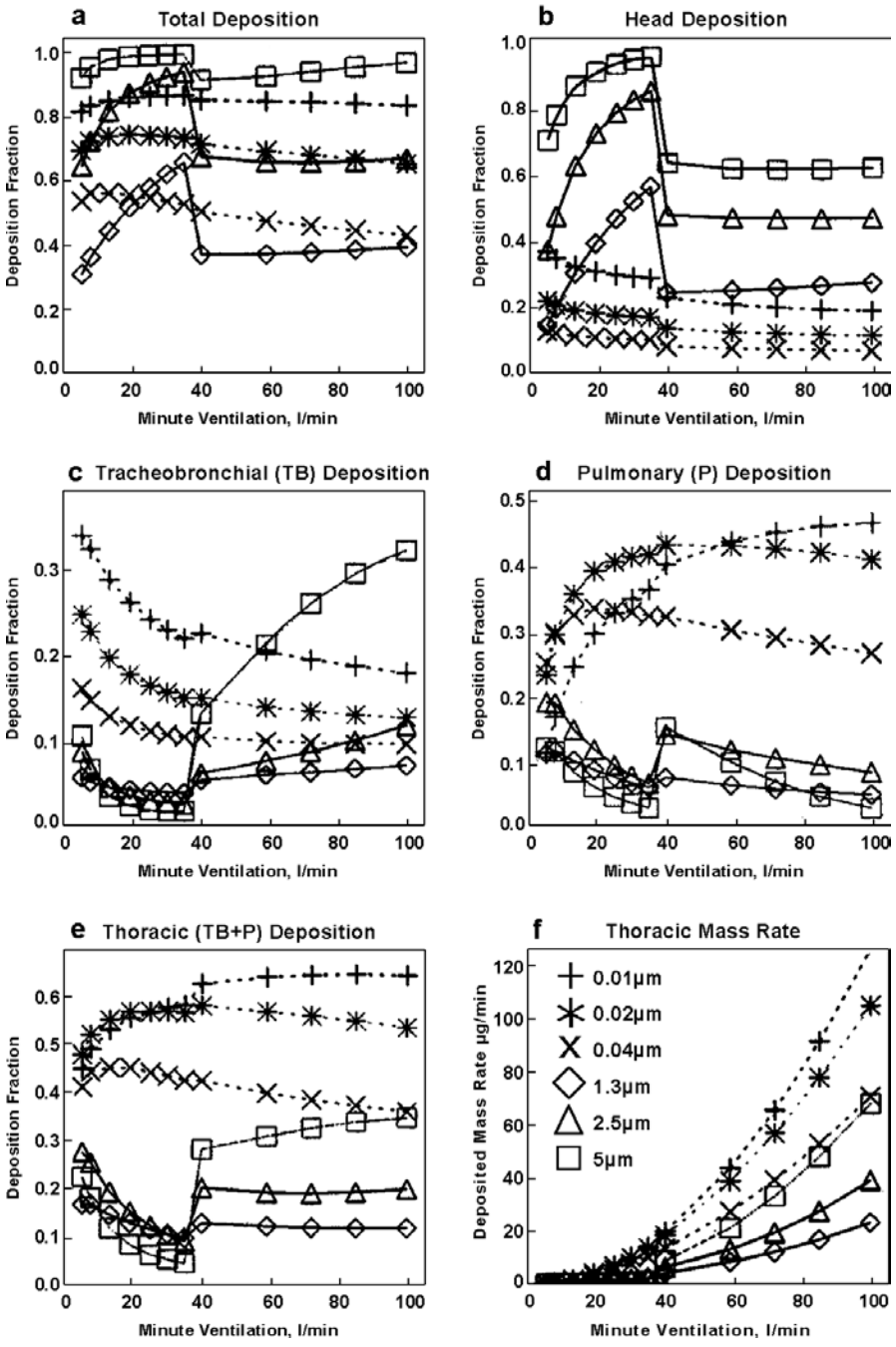

Figure 6-16. Dependency of aerosol deposition in human adults on physical exertion expressed as minute ventilation for different particle sizes. Aerosol concentration used for mass calculation is 140 µg/m^3.

Source: Winter-Sorkina and Cassee (2002).

TABLE 6-5. PARAMETERS USED IN AGE DEPENDENT CALCULATIONS OF THE CIIT/RIVM DEPOSITION MODEL

Age	FRC, mL	URT volume, mL	Breathing frequency, min^{-1}	Tidal volume, mL	Minute ventilation, L/min
3 month	27.36	2.45	39	30.44	1.19
21 month	64.46	6.52	28	81.22	2.27
23 month	78.45	6.94	27	86.79	2.34
27 month	100.67	7.92	26	100.1	2.60
3 years	95.43	9.47	24	121.3	2.91
8+ years	437.34	21.03	17	278.2	4.73
9+ years	513.12	22.44	17	295.8	5.03
14 years	881.47	30.63	16	388.1	6.21
18 years	1,935.34	37.38	15	446.7	6.70
21 years	1,854.54	42.27	14	477.2	6.68

Source: Winter-Sorkina and Cassee (2002).

Results of age-dependent deposition using the parameters given in Table 6-5 are shown in Figure 6-17. The head impaction are based on the data from Becquemin et al. (1991). For coarse particles the adult (here 18 and 21 years old) head deposition fractions are larger than the head deposition fractions in children. The thoracic deposition fraction (which is a sum of tracheobronchial and pulmonary deposition fractions) of ultrafine particles does not change with age. For coarse particles (5 μm and 10 μm) tracheobronchial and thoracic deposition fractions are significantly larger for children (ages of 0-15 years old) than for adults, mainly due to the increase in head deposition from children to adults. The difference in tracheobronchial and thoracic deposition fractions between children and adults increases with particle size.

Pulmonary or alveolar deposition fractions of 5 μm particles for 8-14 years old children are higher than for adults. Deposited aerosol mass rate in the thoracic region increases with age for ultrafine particles. For coarse particles the deposited aerosol mass rate in the thoracic region increases with age up to the age of 14 years. The increase of deposited mass rate is due to the growing tidal volume (Table 6-5). For coarse particles the deposited aerosol mass rate in the thoracic region of 8-14 years old children for 5 μm particles and of 2-14 years old children for 10 μm particles is higher than in adults (18 and 21 years old).

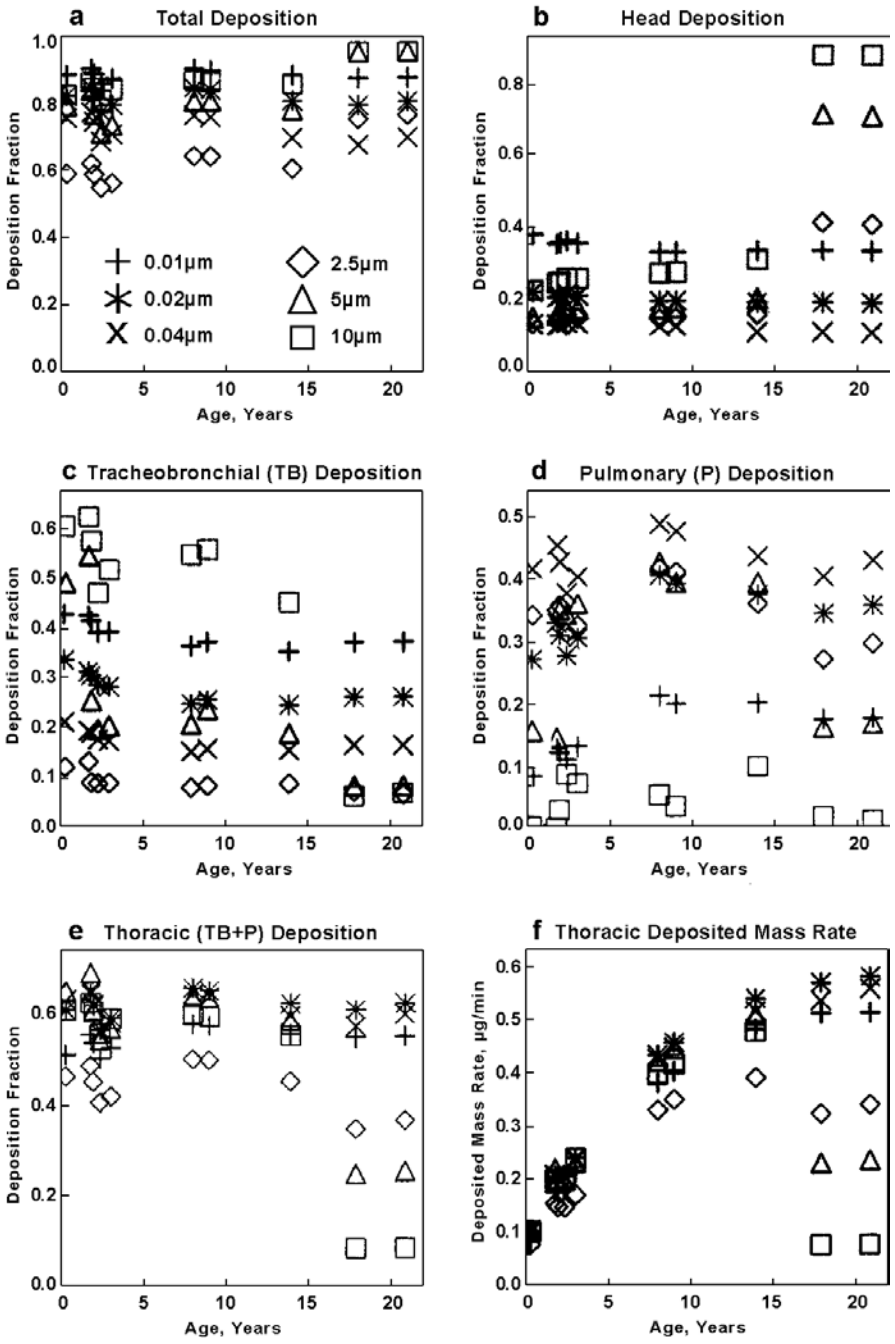

Figure 6-17. Age dependency of human aerosol deposition for different particle sizes. Total (a), head (b), tracheobronchial (c), pulmonary (d) and thoracic (e) deposition fractions, deposited thoracic mass rate (f). Aerosol concentration used for mass calculation is 140 μg/m^3.

Source: Winter-Sorkina and Cassee (2002).

Here it should be emphasized that the age dependency of deposited mass is determined by the age dependencies of head deposition and minute ventilation (tidal volume multiplied by breathing frequency), and that the age dependency of head deposition is based on a limited number of measurements.

It is also useful to examine particle deposition normalized to some parameter such as lung mass, surface area, or number of alveoli. Aerosol deposition normalized to surface area and alveoli is shown in Figure 6-18.

The CIIT/RIVM model calculates lung surface area per airway generation, the first 16 generations belong to the tracheobronchial region. The tracheobronchial lung area, tracheobronchial deposition fractions per unit of surface area and deposited tracheobronchial mass rates per unit surface area are shown in the top of the Figure 6-18. The tracheobronchial surface area grows monotonously from about 197 cm^2 at birth to about 1,554 cm^2 at the age of 21 years. Tracheobronchial deposition fractions per unit surface area are decreasing with age for all particle sizes due to increasing tracheobronchial lung area with age. Tracheobronchial deposition fractions per unit surface area are up to 10 times (for ultrafine particles) and 68 times (for coarse particles) higher for 3 month old babies compared to adults; up to 4 times (ultrafine) and 27 times (coarse) higher for the age of 2 years compared to adults. For ultrafine particles the deposited aerosol mass rates in tracheobronchial region per unit surface area for 3 month old babies are up to 1.8 times larger than for adults and seem to decrease monotonously with progressing age. However, small deviation in tracheobronchial surface area at the age of 2.3 and 3 years, due to the differences in lung geometry, leads to almost same tracheobronchial deposited mass rates per unit surface area as for adults. For coarse particles of 2.5 µm, 5 µm and 10 µm the deposited aerosol mass rates in tracheobronchial region per unit surface area for 3 month old babies are respectively 2.5, 8, and 12 times larger than for adults, for 2.3 years old children respectively 1.2, 2.2, and 6.2 times larger than for adults, and for 8 years old children respectively 1.7, 3.5, and 11 times larger than for adults. The age dependency of tracheobronchial deposited mass per unit surface area is determined by the age dependencies of head deposition, minute ventilation, and tracheobronchial surface area.

The total number of alveoli, pulmonary deposition fractions per alveolus and deposited pulmonary mass rates per alveolus as a function of age are shown in the bottom part of the Figure 6-18. There are approximately $50 \bullet 10^6$ alveoli at birth and about 85% of alveoli are added after birth, the adult number of about $300 \bullet 10^6$ is attained by 20 years (Mauderly,

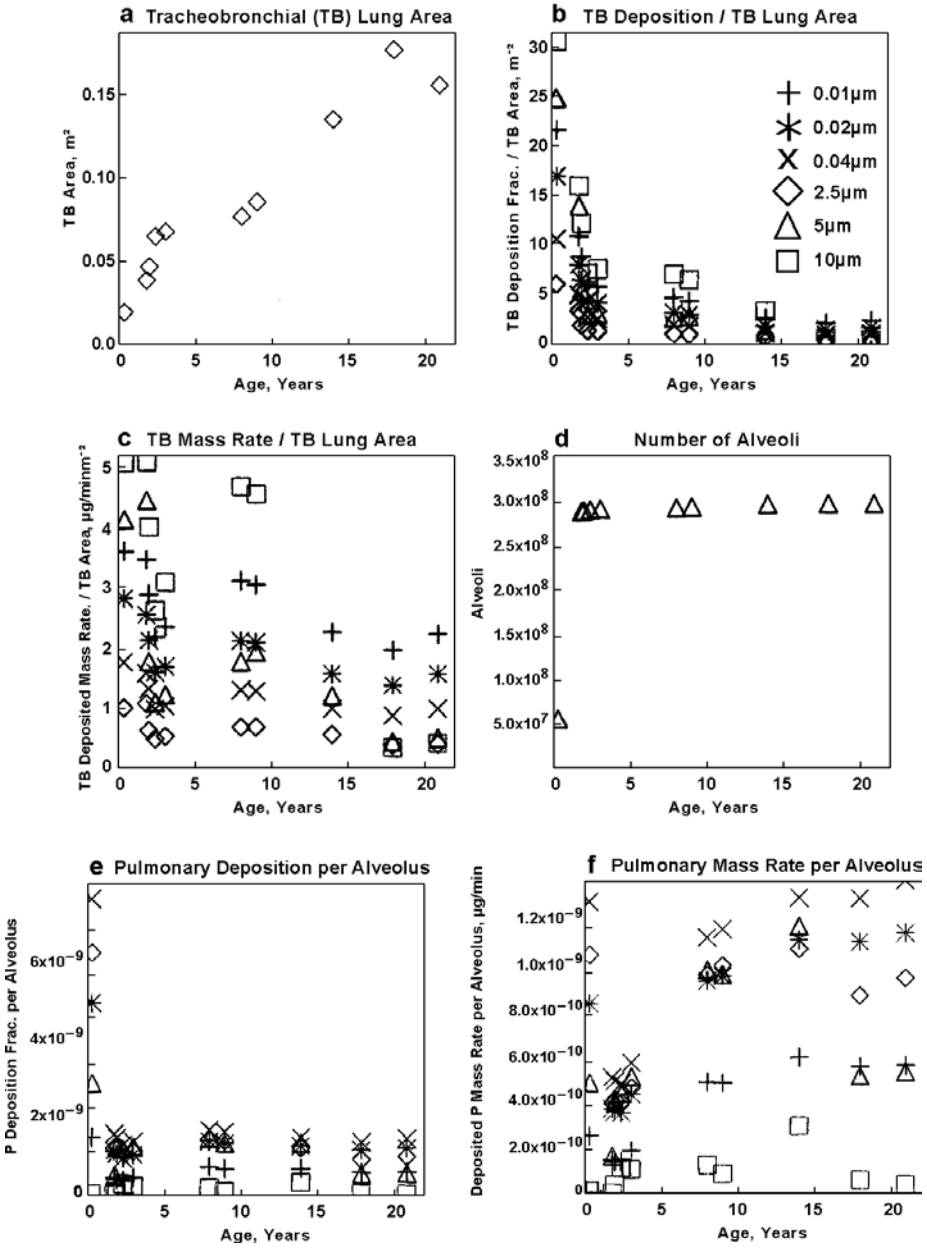

Figure 6-18. Age dependency of human standardized aerosol deposition for different particle sizes. Tracheobronchial (TB) lung area (a), TB deposition fraction per unit of TB lung area (b), deposited TB mass rate per unit of TB lung area (c), total number of alveoli (d), pulmonary (P) deposition fraction per alveolus (e), deposited P mass rate per alveolus (f). Aerosol concentration used for mass calculation is 140 µg/m^3.

Source: Winter-Sorkina and Cassee (2002).

1979). Alveolar multiplication is extremely rapid in the first few years of life and then slows down. Pulmonary deposition fractions per alveolus are up to 5 times (for ultrafine particles) and 6 times (for coarse particles) higher for 3 month old babies compared to adults. For children of the age of about 2 years and older the pulmonary deposition fraction per alveolus does not change significantly. Deposited pulmonary mass rates per alveolus are lower for the age of 2-3 years compared to adults for ultrafine and 2.5 μm particles and 1.8 to 2.2 times higher for 8-14 years old children compared to adults for 5 μm particles. The age dependency of pulmonary deposition per alveolus is determined by the age dependencies of head deposition, minute ventilation, and alveolar multiplication.

Alveolar surface area obtained from 8 normal adult human lungs by Gehr et al. (1978) is 143 ± 12 in^2. The airway surface area for generations above 16 belonging to the pulmonary 2 region calculated from the model is 9.35 m^2. Therefore, the adult tracheobronchial deposition fraction and mass rate per unit surface area are 2,078 to 377 times (for 0.01 μm to 0.04 μm particles) and 223 to 6,238 times (for 2.5 μm to 10 μm particles) larger than adult pulmonary deposition fraction and mass rate per unit surface area. Progressive morphological changes in the senescent adult lung result primarily in a loss of alveolar surface area and altered elastic properties. Alveolar septal membranes weaken and stretch, causing an enlargement of alveoli and a reduced surface area. Changes occurring in the alveolar septal wall result in a nearly linear decrease of surface area between the ages of 20 and 80 years, such that by 80 years the surface area is reduced by approximately 30% (Mauderly, 1979). There is little age-related change of breathing patterns of adults at rest although there is a slight trend toward a larger minute ventilation with age. The minute ventilation during exercise increases with age (Mauderly, 1979). Thus, the pulmonary deposition fraction, mass rate and deposited mass per unit surface area increase nearly linear between the ages of 20 and 80 years by approximately 30%.

6.6.4.3 Comparisons of Deposition in Humans and Rats

Dosimetric issues are important in the use of animal to human extrapolation in risk assessment. The MPPD model was used to compare deposition in humans and rats. The MPPD model uses the multiple-path aerosol deposition model for a rat (Anjilvel and Asgharian, 1995) which incorporates asymmetry in the lung branching structure and calculates deposition at the individual airway level. Deposition calculations were performed with the 5 lobe lung model for humans for light exercise. Respiratory parameters used in the model runs are shown in Table 6-6. The percent deposition for human mouth breathing, human nasal breathing, and rat nasal breathing (rats are obligate nose breathers) are shown in Figure 6-19a, b, and c for ET, TB,

TABLE 6-6. RESPIRATORY PARAMETERS FOR HUMANS AND RATS

	Breaths min^{-1}	Tidal Volume mL	FRM mL	URT mL	Lung mass g
Rat	102	2.1	4	.42	4.34
Human	20	1,250	3,300	50	1,100

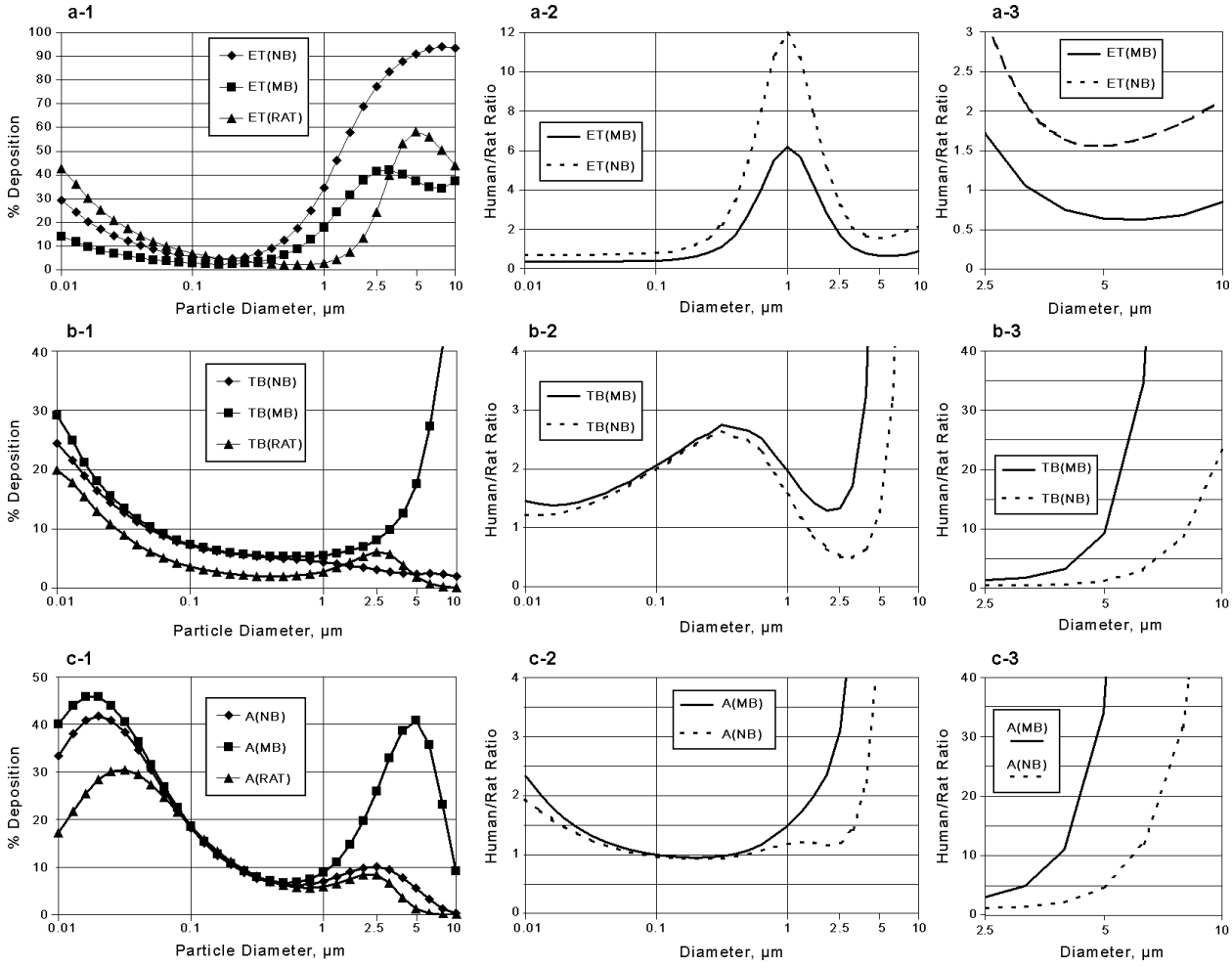

Figure 6-19. Comparison of percent deposition for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat for nasal and mouth breathing humans for the ET (a), TB (b), and A (c) regions of the respiratory tract.

and A deposition. Figure 6-19 also shows the ratios of percent deposition for human to rat for mouth breathing and nasal breathing humans.

ET deposition is shown in Figure 6-19a. Deposition of coarse mode particles in the ET region increases significantly with particle size because of impaction. However, increased inertia poses a limitation to the ability of particles to enter the ET region. This reduction in the inhaled fraction of the aerosol is relevant for particle sizes larger than 3-4 μm for rats and sizes larger than about 8 μm for humans and is more significant for rats than for humans. The inhalability adjustment (Menache et al., 1995) used in the MPPD model does not change deposition results for humans significantly, the tracheobronchial deposition fraction reduces 3.5% and thoracic deposition fraction 2.5% for 10 μm particles. For rats accounting for inhalability reduces the nasal deposition fraction about 1.5 times for 5 μm particles and more than 2 times for 10 μm particles. As a result tracheobronchial and pulmonary deposition fractions are reduced about 25% for 5 μm particles. ET percent deposition is greater for humans than rats, above about 0.15 μm for nose breathing and 0.3 μm for mouth breathing, except that for mouth breathing, human percent deposition drops below that of rats at about 3 μm. This leads to a peak in the human/rat ratio at 1 μm. The fraction TB percent deposition (Figure 6-19b) is much lower for rats than humans in the accumulation mode size range. However, between 1.5 and 5 μm the percent deposition for the rat is greater than that for the nasal breathing human. Above about 2.5 μm, the percent deposition for the mouth breathing human increases rapidly relative to that of the rat. For A deposition (Figure 6-19c), rats and humans have almost the same percent deposition in the accumulation mode region. However, the percent deposition for the nasal breathing human and the rat fall off for particles above about 2.5 μm, the rat more rapidly than the human. These differences are borne out in the human/rat ratios which become very high for particles above 2.5 μm.

The percent deposition values for human and rat, shown in Figure 6-19, can be used with respiratory parameters and respiratory tract surface areas or lung mass to normalize deposition to lung mass, TB surface area, or A surface area provided those parameters are known.

Figure 6-20a compares deposition of PM by size in humans and rats normalized to lung mass for thoracic (TH = TB + A) deposition. The deposition, in terms of μg of PM deposited per gram of lung is greater for humans than rats for particles below about 2 μm for mouth breathing humans and for particles below about 5 μm for nasal breathing humans. As can be seen in 6-20b and c,

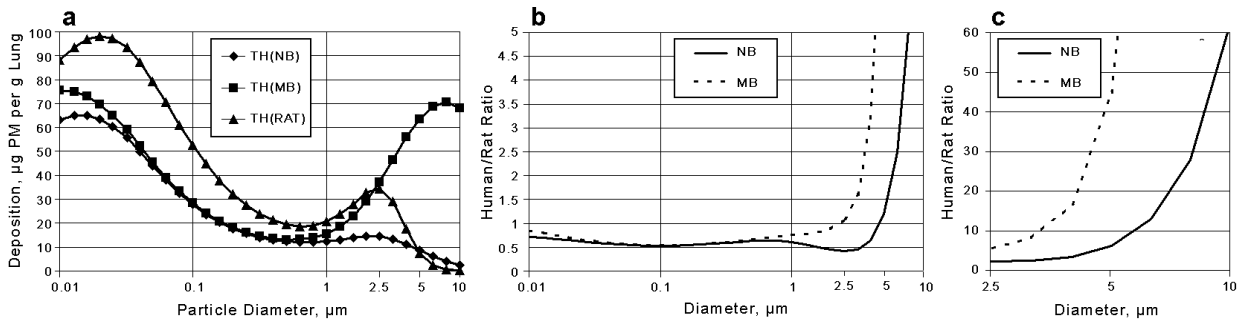

Figure 6-20. Normalized deposition patterns for rats (nasal breathing) and humans (nasal and mouth breathing and the ratio of human to rat for nasal and mouth breathing humans for the thoracic region (in terms of µg PM per g of lung). Quantity of PM deposited based on 8 hour exposure to 100 µg/m^3.

the ratio of human to rat deposition, especially for mouth breathing, increases to very high values for particles above about 2.5 µm.

From the above comparison of rats and humans, it would appear that for inhalation studies with accumulation mode aerosols, as might be done using concentrated air particles, equivalent TH deposition in rats could be obtained with 0.5 to 0.75 of concentrations for humans. However, for coarse particles the deposition ratios are very sensitive to particle size. Thus, for coarse particles resuspended from bulk material particle size distribution measurements would be needed and very high concentration ratio might be needed for equivalent deposition on a per gram of lung basis.

There is some variation in the reported values for the surface areas of the various portions of the human and rat respiratory tract as listed in Table 6-7. The results using the U.S. EPA default surface areas are shown in Figure 6-21. For TB deposition in terms of µg of PM per cm^2 of bronchial surface, shown in Figure 6-21a, the human percent deposition is greater than that of the rat except for particles between about 1.5 and 5 µm. In this size range the rat deposition is greater than that of the nasal breathing human. Again, the ratio increases rapidly, especially for mouth breathing and for larger particles. The A deposition (Figure 6-21b) for nasal breathing humans and rats is similar — between 0.05 and 3 µm with rat deposition dropping for particles above 3 µm. However, the ratios increase above 3 µm and rapidly above 5 µm.

TABLE 6-7. SURFACE AREAS OF TRACHEOBRONCHIAL AND ALVEOLAR REGIONS FOR HUMANS AND RATS

Surface Areas

	Human		Rat		Human/Rat Ratios	
	TB	A	TB	A	TB	A
EPA Default [a]	.269	54	.00225	0.34	119.6	158.8
CIIT/RIVM Model [b]	.1554 [c]	150.3 [d]	.00124 [e]	.55 [c]	125.3	273.3

[a] U.S. EPA (1996) based on U.S. EPA 1994).
[b] As reported in Winter-Sorkina and Cassee (2002).
[c] Mauderly (1979).
[d] Gehr et al. (1978). (143 m^2 alveolar + 7.3 m^2 respiratory bronchioles).
[e] Calculated from human/rat ratio in Winter-Sorkina and Casse (2002).

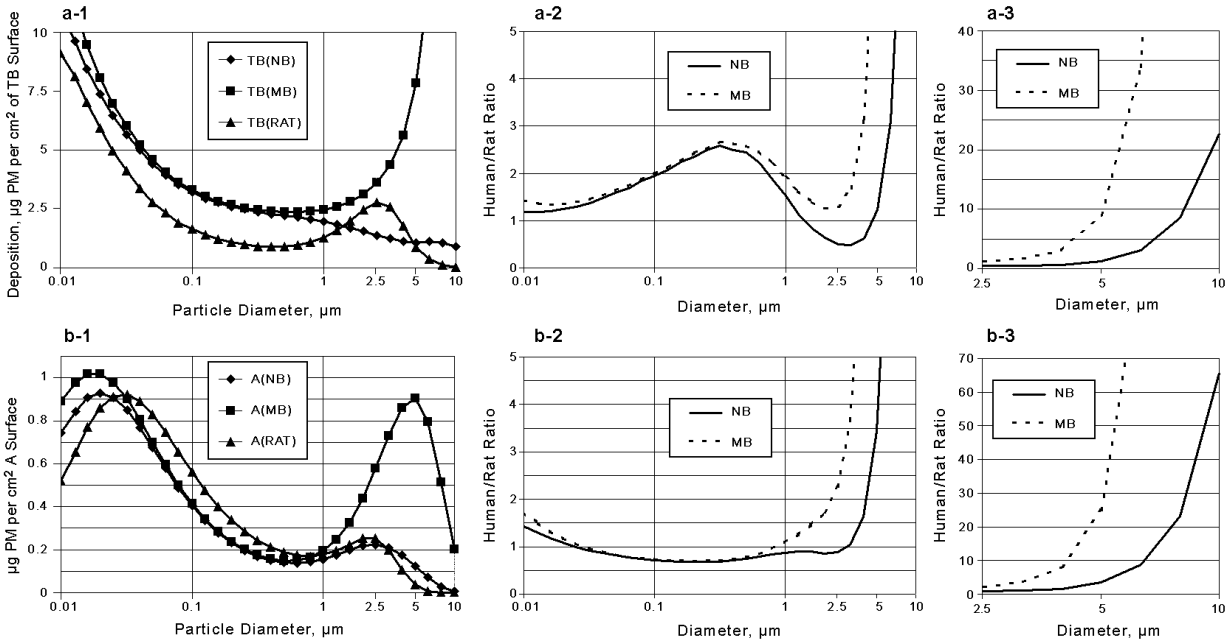

Figure 6-21. Normalized deposition patterns arising from 8 hr exposure to 100 µg/m^3, based on EPA default values of surface area, for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat (a) for the TB region (in units of µg PM per m^2 TB area) and (b) for the A region (in terms of µg PM per m^2 of A).

The results using the CIIT/RIVM surface area values are shown in Figure 6-22. As would be expected for the changes in surface area, the TB deposition amounts are larger and the A deposition amounts are smaller (Figure 6-22a-1 and 22b-1) and the A deposition for mouth breathing is not as much greater for humans than rats for coarse particles. However, the ratios (Figure 22a-2,3 and 22b-2,3) are not greatly different.

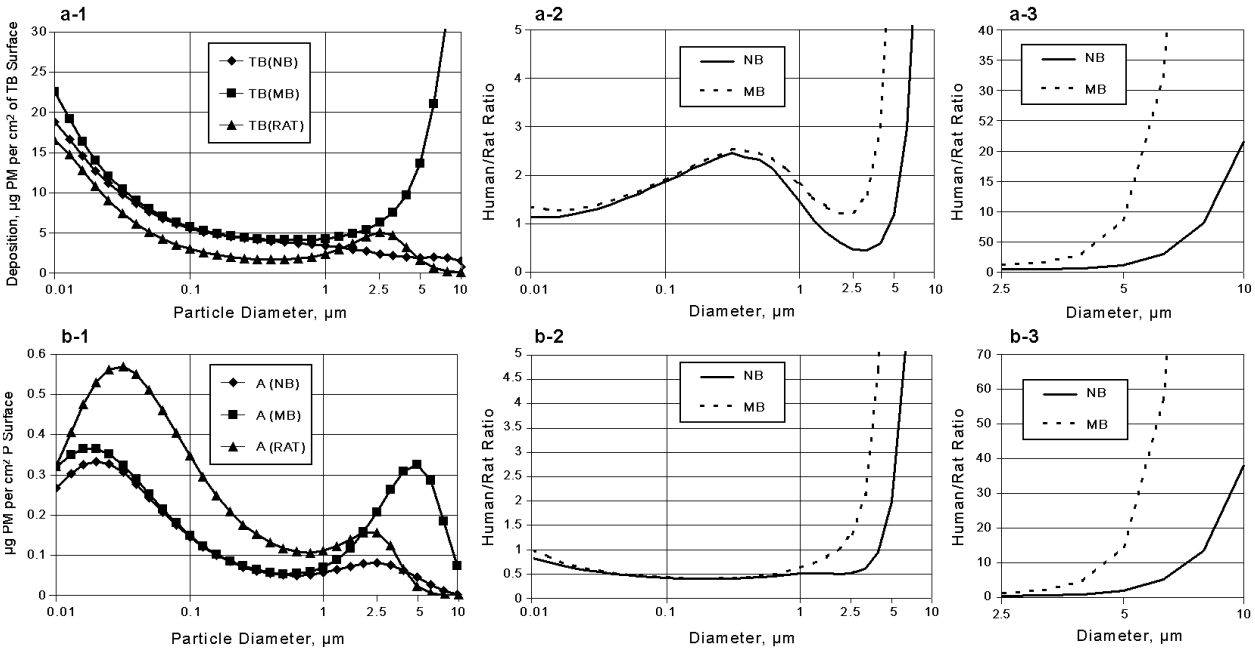

Figure 6-22. Normalized deposition patterns arising from 8 hr exposure to 100 µg/m^3, based on surface area values from Winter-Sorkina and Cassee (2002), for rats (nasal breathing) and humans (nasal and mouth breathing) and the ratio of human to rat (a) for the TB region (in units of µg PM per m^2 TB area) and (b) for the A region (in terms of µg PM per m^2 of A).

The human/rat comparisons, whether normalized by lung mass or by either sets of surface areas, indicate that for fine particles normalized human and rat deposition are comparable. However, for coarse particles much higher exposures may be required for rats to obtain equivalent normalized doses.

6.7 SUMMARY AND CONCLUSIONS

6.7.1 Particle Dosimetry

Understanding the mechanisms of action and ultimate biological effects of inhaled particulate matter requires knowledge of the dosimetry of such material. This is because the proximal cause of the biological response is the dose of particles delivered to and retained at the target site, rather than the exposure concentration. Deposition, clearance, translocation, and retention comprise the essential elements of dosimetry.

Dosimetry of inhaled particles is essential for extrapolating effects found in controlled exposure studies of laboratory animals to those observed in human exposure studies, and for relating effects in healthy individuals to those in potentially susceptible persons.

Understanding of total deposition as a function of particle size and breathing pattern and of certain aspects of regional deposition of particles has improved since publication of the 1996 PM AQCD. The ET region, especially the nasal passages, is a moderately efficient filter for ultrafine and coarse particles. Accordingly, particles removed in the ET region are not available for deposition in the TB and A regions of the respiratory tract. Within the thoracic region, the deposition distribution of ultrafine particles is highly skewed towards the proximal airway regions and resembles that of coarse particles. Thus, the deposition patterns for ultrafine particles are similar to those of coarse-mode particles with significant fractional deposition in all three regions. Particles in the accumulation mode size range (0.1 to 1.0 μm) have low fractional deposition in all three regions.

6.7.2 Host Factors

Certain host factors have a marked effect on particle dosimetry and can affect the biological response to inhaled particulate matter.

Gender

There are significant gender differences in the homogeneity of deposition as well as the deposition rate of particles. These differences derive from differences between males and females in body size, conductive airway size, and ventilatory parameters. Females have a greater deposition of coarse mode particles in the ET and TB regions, and lower deposition in the A region. This gender effect appears to be particle size dependent showing a greater

fractional deposition in females for very small ultrafine and large coarse particles. Total fractional lung deposition for 0.04 and 0.06 μm particles also appears to be greater in females than males but only negligibly so for particles in the size range 0.8 – 1.0 μm. As the particle size increases (3 to 5 μm), total fractional deposition increases in females. While deposition appears to be more localized in females than males, deposition rate appears to be greater in males.

Exercise

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

Age

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

Lung Disease

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

6.7.3 Laboratory Animal Studies

It is difficult to systematically compare deposition patterns in laboratory animals used in dosimetric studies. Deposition patterns are similar between laboratory animals and humans but there are absolute differences in deposition fractions. In most laboratory animal species, deposition in the ET region is near 100% for particles greater than 5 μm, indicating greater efficiency than that seen in humans. In the TB region, there is a relatively constant, but lower deposition fraction for particles greater than 1 μm compared to humans. Finally, in the A region, deposition fraction peaks at a lower particle size (~1 μm) in laboratory animals than in humans.

Clearance processes are similar in animals and humans but the clearance rate for particles is typically faster in laboratory animals.

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

6.7.4 Mathematical Models

There has been significant improvement in the mathematical and computational fluid dynamic modeling of particle dosimetry in the respiratory tract of humans. Although the models have become more sophisticated and adaptable, validation of the models by experimental data is still required.

Key Points

- Dosimetry establishes the relationship between PM exposure and the dose of PM delivered to and retained at the target site. Deposition, clearance, translocation, and retention comprise the essential elements of dosimetry.

- Dosimetric information is critical to extrapolating effects found in controlled exposure studies of laboratory animals to those observed in human exposure studies and for relating effects in normal healthy persons to those in potentially susceptible persons.
- Dosimetry separates the respiratory tract into three regions, extrathoracic (ET), tracheobronchial (TB), and alveolar (A), based on anatomical features and particle deposition and clearance phenomena that occur within each region.
- Particles in the accumulation mode size range (0.1 to 1.0 μm D_p) have the lowest deposition fraction in all three regions.
- Coarse and ultrafine particles have higher fractional deposition. For coarse particles, fractional deposition peaks between 5 and 10 μm D_p for the TB region and 2.5 and 5 μm D_p for the A region.
- For ultrafine particles, fractional deposition peaks between 0.0025 and 0.005 μm D_p for the TB region and between 0.01 and 0.05 for the A region.
- A significant fraction of ultrafine and coarse particles, but not particles in the accumulation-mode size range, are deposited in the ET region.
- Once particles are deposited on the surface of the airways, they are subsequently cleared from the respiratory tract completely or translocated to other sites within the system by distinct regional processes. Ultrafine particles can be rapidly cleared from the lungs into the systemic circulation where they can be transported to extrapulmonary regions. Such transport could provide a mechanism whereby particles could affect cardiovascular function as reported in the epidemiologic studies
- Fractional deposition, as a function of particle size, depends on lung size, tidal volume, and breathing rate. Exercising subjects receive higher doses of particles per cm^2 of lung surface than subjects at rest.
- Airway structure and physiological function vary with age. Such variations may alter the deposition patterns for inhaled particles. Airflow distribution is very uneven in diseased lungs, and deposition can be enhanced locally in areas of active ventilation. Total lung deposition is generally increased by obstructed airways so that particle deposition is enhanced in people with chronic lung disease. Unfortunately, deposition studies in another susceptible population, the elderly, are still lacking.

- Computational models allow calculation of fractional deposition and dose per cm^2 of lung surface as a function of particle size and respiratory parameters for humans and some animals (including the laboratory rat). Such calculations can be used to predict the exposures needed to produce comparable doses for animal to human extrapolation.
- Computational models have been improved in recent years but experimental validation of model predictions is still required.

REFERENCES

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

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

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

Adgate, J. L.; Ramachandran, G.; Pratt, G. C.; Waller, L. A.; Sexton, K. (2002) Spatial and temporal variability in outdoor, indoor, and personal PM2.5 exposure. Atmos. Environ. 36: 3255-3265.

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

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

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

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

Asgharian, B.; Miller, F. J.; Subramaniam, R. P. (1999) Dosimetry software to predict particle deposition in humans and rats. CIIT Activities 19(3). Available: http://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.

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

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

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

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

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

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

Bennett, W. D.; Zeman, K. L.; Kang, C. W.; Schechter, M. S. (1997a) Extrathoracic deposition of inhaled, coarse particles (4.5 μm) in children vs. adults. In: Cherry, N.; Ogden, T., eds. Inhaled particles VIII: proceedings of an international symposium on inhaled particles 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 of lung volume. J. Appl. Physiol. 86: 168-173.

Benson, J. M.; Henderson, R. F.; McClellan, R. O.; Hanson, R. L.; Rebar, A. H. (1986) Comparative acute toxicity of four nickel compounds to F344 rat lung. Fundam. Appl. Toxicol. 7: 340-347.
Brauer, M.; Avila-Casado, C.; Fortoul, T. I.; Vedal, S.; Stevens, B.; Churg, A. (2001) Air pollution and retained particles in the lung. Environ. Health Perspect. 109: 1039-1043.
Broday, D. M.; Georgopoulos, P. G. (2001) Growth and deposition of hygroscopic particulate matter in the human lungs. Aerosol Sci. Technol. 34: 144-159.
Brody, A. R.; Roe, M. W. (1983) Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. Am. Rev. Respir. Dis. 128: 724-729.
Brody, A. R.; Hill, L. H.; Adkins, B., Jr.; O'Connor, R. W. (1981) Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. Am. Rev. Respir. Dis. 123: 670-679.
Brown, J. S.; Kirby, Z. L.; Bennett, W. D. (2001) Regional deposition of coarse particles and ventilation distribution in healthy subjects and patients with cystic fibrosis. J. Aerosol Med. 14: 443-454.
Brown, J. S.; Zeman, K. L.; Bennett, W. D. (2002) Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am. J. Respir. Crit. Care Med. 166: 1240-1247.
California Air Resources Board. (1987) Ambient air quality standard for ozone: health and welfare effects. Sacramento, CA: California Air Resources Board.
Camner, P.; Anderson, M.; Philipson, K.; Bailey, A.; Hashish, A.; Jarvis, N.; Bailey, M.; Svartengren, M. (1997) Human bronchiolar deposition and retention of 6-, 8-, and 10-μ particles. Exp. Lung Res. 23: 517-535.
Chang, Y. H.; Yu, C. P. (1999) A model of ventilation distribution in the human lung. Aerosol Sci. Technol. 30: 309-319.
Cheng, Y.-S.; Smith, S. M.; Yeh, H.-C.; Kim, D.-B.; Cheng, K.-H.; Swift, D. L. (1995) Deposition of ultrafine aerosols and thoron progeny in replicas of nasal airways of young children. Aerosol. Sci. Technol. 23: 541-552.
Cheng, K.-H.; Cheng, Y.-S.; Yeh, H.-C.; Guilmette, R. A.; Simpson, S. Q.; Yang, Y.-H.; Swift, D. L. (1996) *In vivo* measurements of nasal airway dimensions and ultrafine aerosol deposition in the human nasal and oral airways. J. Aerosol Sci. 27: 785-801.
Cheng, K.-H.; Cheng, Y.-S.; Yeh, H.-C.; Swift, D. L. (1997) An experimental method for measuring aerosol deposition efficiency in the human oral airway. Am. Ind. Hyg. Assoc. J. 58: 207-213.
Churg, A.; Brauer, M. (1997) Human lung parenchyma retains $PM_{2.5}$. Am. J. Respir. Crit. Care Med. 155: 2109-2111.
Churg, A.; Vedal, S. (1996) Carinal and tubular airway particle concentrations in the large airways of non-smokers in the general population: evidence for high particle concentration at airway carinas. Occup. Environ. Med. 53: 553-558.
Cohen, B. S.; Harley, N. H.; Schlesinger, R. B.; Lippmann, M. (1988) Nonuniform particle deposition on tracheobronchial airways: implications for lung dosimetry. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fisher, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32 (suppl. 1): 1045-1053.
Cohen, B. S.; Sussman, R. G.; Lippmann, M. (1990) Ultrafine particle deposition in a human tracheobronchial cast. Aerosol Sci. Technol. 12: 1082-1091.
Cohen, B. S.; Xiong, J. Q.; Fang, C.-P.; Li, W. (1998) Deposition of charged particles on lung airways. Health Phys. 74: 554-560.
Comer, J. K.; Kleinstreuer, C.; Hyun, S.; Kim, C. S. (2000) Aerosol transport and deposition in sequentially bifurcating airways. J. Biomech. Eng. 122: 152-158.
Comer, J. K.; Kleinstreuer, C.; Zhang, Z. (2001a) Flow structures and particle deposition patterns in double bifurcation airway models. Part 1. Air flow fields. J. Fluid Mech. 435: 24-54.
Comer, J. K.; Kleinstreuer, C.; Kim, C. S. (2001b) Flow structures and particle deposition patterns in double bifurcation airway models. Part 2. Aerosol transport and deposition. J. Fluid Mech. 435: 55-80.
Crapo, J. D.; Barry, B. E.; Gehr, P.; Bachofen, M.; Weibel, E. R. (1982) Cell characteristics of the normal human lung. Am. Rev. Respir. Dis. 125: 740-745.
Crystal, R. G., West, J. B.; Barnes, P. J.; Weibel, E. R., eds. (1997) The lung: scientific foundations. Volume 1. Section III: major components. 2nd ed. Philadelphia, PA: Lippincott-Raven; chapters 30-67, pp. 445-991.
Cuddihy, R. G. (1984) Mathematical models for predicting clearance of inhaled radioactive materials. In: Smith, H.; Gerber, G., eds. Lung modelling for inhalation of radioactive materials: proceedings of a meeting jointly organized by the Commission of the European Communities and the National Radiological Protection Board; March; Oxford, United Kingdom. Luxembourg: Commission of the European Communities; pp. 167-179; report no. EUR 9384 EN.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Harmsen, A. G.; Muggenburg, B. A.; Snipes, M. B.; Bice, D. E. (1985) The role of macrophages in particle translocation from lungs to lymph nodes. Science (Washington, DC) 230: 1277-1280.

Heistracher, T.; Hofmann, W. (1995) Physiologically realistic models of bronchial airway bifurcation. J. Aerosol Sci. 26: 497-509.

Heistracher, T.; Hofmann, W. (1997) Flow and deposition patterns in successive airway bifurcations. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl.): 537-542.

Henderson, R. F.; Driscoll, K. E.; Harkema, J. R.; Lindenschmidt, R. C.; Chang, I.-Y.; Maples, K. R.; Barr, E. B. (1995) A comparison of the inflammatory response of the lung to inhaled versus instilled particles in F344 rats. Fundam. Appl. Toxicol. 24: 183-197.

Henshaw, D. L.; Fews, A. P. (1984) The microdistribution of alpha emitting particles in the human lung. In: Smith, H.; Gerber, G., eds. Lung modelling for inhalation of radioactive materials: proceedings of a meeting jointly organized by the Commission of the European Communities and the National Radiological Protection Board; March; Oxford, United Kingdom. Luxembourg: Commission of the European Communities; pp. 199-218; report no. EUR 9384 EN.

Heyder, J.; Rudolf, G. (1977) Deposition of aerosol particles in the human nose. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 1; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 107-126.

Hiller, F. C. (1991) Health implications of hygroscopic particle growth in the human respiratory tract. J. Aerosol Med. 4: 1-23.

Hinds, W. C. (1999) Aerosol technology: properties, behavior, and measurement of airborne particles. 2nd ed. New York, NY: John Wiley & Sons.

Hofmann, W.; Bergmann, R. (1998) Predictions of particle deposition patterns in human and rat airways. Inhalation Toxicol. 10: 557-583.

Hofmann, W.; Martonen, T. B.; Graham, R. C. (1989a) Predicted deposition of nonhygroscopic aerosols in the human lung as a function of subject age. J. Aerosol Med. 2: 49-68.

Hofmann, W.; Koblinger, L.; Martonen, T. B. (1989b) Structural differences between human and rat lungs: implications for Monte Carlo modeling of aerosol deposition. In: Mahaffey, J. A., ed. 26th Hanford life sciences symposium, modeling for scaling to man: biology, dosimetry, and response. Health Phys. 57(suppl. 1): 41-47.

Hofmann, W.; Balásházy, I.; Heistracher, T.; Koblinger, L. (1996) The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. Aerosol Sci. Technol. 25: 305-327.

Hofmann, W.; Bergmann, R.; Koblinger, L. (1999) Characterization of local particle deposition patterns in human and rat lungs by different morphometric parameters. J. Aerosol Sci. 30: 651-667.

Hofmann, W.; Asgharian, B.; Bergmann, R.; Anjilvel, S.; Miller, F. J. (2000) The effect of heterogeneity of lung structure on particle deposition in the rat lung. Toxicol. Sci. 53: 430-437.

Hsieh, T. H.; Yu, C. P. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhalation Toxicol. 10: 121-130.

Huchon, G. J.; Montgomery, A. B.; Lipavsky, A.; Hoeffel, J. M.; Murray, J. F. (1987) Respiratory clearance of aerosolized radioactive solutes of varying molecular weight. J. Nucl. Med. 28: 894-902.

International Commission on Radiological Protection. (1960) Report of Committee II on permissible dose for internal radiation (1959). Health Phys. 3.

International Commission on Radiological Protection. (1979) Limits for intakes of radionuclides by workers. Oxford, United Kingdom: Pergamon Press; ICRP publication 30, part 1.

International Commission on Radiological Protection. (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, pp. 1-482.).

Jaques, P. A.; Kim, C. S. (2000) Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhalation Toxicol. 12: 715-731.

John, J.; Wollmer, P.; Dahlbäck, M.; Luts, A.; Jonson, B. (1994) Tidal volume and alveolar clearance of insoluble particles. J. Appl. Physiol. 76: 584-588.

Katz, I. M. (2001) Computer modeling of fluid dynamics and particle motion in the larynx and trachea. In: Martonen, T. B., ed. Medical Applications of Computer Modeling: The Respiratory System. Boston, MA: WIT Press, pp. 47-63.

Katz, I. M.; Martonen, T. B. (1996) Three-dimensional fluid particle trajectories in the human larynx and trachea. J. Aerosol Med. 9: 513-20.

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.
Kaye, S. R.; Phillips, C. G.; Winlove, C. P. (2000) Measurement of non-uniform aerosol deposition patterns in the conducting airways of the porcine lung. J. Aerosol Sci. 31: 849-866.
Kesavanathan, J.; Swift, D. L. (1998) Human nasal passage particle deposition: the effect of particle size, flow rate, and anatomical factors. Aerosol Sci. Technol. 28: 457-463.
Keyhani, K.; Scherer, P. W.; Mozell, M. M. (1995) Numerical simulation of airflow in the human nasal cavity. J. Biomech. Eng. 117: 429-41.
Kim, C. S. (2000) Methods of calculating lung delivery and deposition of aerosol particles. Respir. Care 45: 695-711.
Kim, C. S.; Fisher, D. M. (1999) Deposition characteristics of aerosol particles in sequentially bifurcating airway models. Aerosol Sci. Technol. 31:198-220.
Kim, C. S.; Garcia, L. (1991) Particle deposition in cyclic bifurcating tube flow. Aerosol Sci. Technol. 14: 302-315.
Kim, C. S.; Hu, S. C. (1998) Regional deposition of inhaled particles in human lungs: comparison between men and women. J. Appl. Physiol. 84: 1834-1844.
Kim, C. S.; Iglesias, A. J. (1989) Deposition of inhaled particles in bifurcating airway models: I. inspiratory deposition. J. Aerosol Med. 2: 1-14.
Kim, C. S.; Jaques, P. A. (2000) Respiratory dose of inhaled ultrafine particles in healthy adults. Phil. Trans. Roy. Soc. London A 358: 2693-2705.
Kim, C. S.; Kang, T. C. (1997) Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am. J. Respir. Crit. Care Med. 155: 899-905.
Kim, C. S.; 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.
Kodavanti, U. P.; Schladweiler, M. C. J.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; Samet, J. M.; McGee, J.; Richards, J. H.; Costa, D. L. (2002) Pulmonary and systemic effects of zinc-contining emission particles in three rat strains: multiple exposure scenarios. Toxicol. Sci. 70: 73-85.
Kohlhäufl, M.; Brand, P.; Scheuch, G.; Meyer, T. S.; Schulz, H.; Häussinger, K.; Heyder, J. (1999) Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. Am. J. Respir. Crit. Care Med. 159: 902-906.
Kreyling, W. G. (1992) Intracellular particle dissolution in alveolar macrophages. Environ. Health Perspect. 97 :121-126.
Kreyling, W. G.; Blanchard, J. D.; Godleski, J. J.; Haeussermann, S.; Heyder, J.; Hutzler, P.; Schulz, H.; Sweeney, T. D.; Takenaka, S.; Ziesenis, A. (1999) Anatomic localization of 24- and 96-h particle retention in canine airways. J. Appl. Physiol. 87: 269-284.
Kreyling, W. G.; Semmler, M.; Erbe, F.; Mayer, P.; Takenaka, S.; Schulz, H.; Oberdorster, G.; Ziesenis, A. (2002) Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J. Toxicol. Environ. Health Part A 65: 1513-1530.
Kuempel, E. D. (2000) Comparison of human and rodent lung dosimetry models for particle clearance and retention. Drug Chem. Toxicol. 23: 203-222.
Kuempel, E. D.; O'Flaherty, E. J.; Stayner, L. T.; Smith, R. J.; Green, F. H. Y.; Vallyathan, V. (2001a) A biomathematical model of particle clearance and retention in the lungs of coal miners. I. Model development. Regul. Toxicol. Pharmacol. 34: 69-87.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Martonen, T. B.; 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.; Zhang, Z; Yu, G.; Musante, C. J. (2001a) Three-dimensional computer modeling of the human upper respiratory tract. Cell Biochem. Biophys. 35: 255-261.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001b) Fluid dynamics in airway bifurcations: I. Primary flows. Inhalation Toxicol. 13: 261-79.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001c) Fluid dynamics in airway bifurcations: II. Secondary currents. Inhalation Toxicol. 13: 281-9.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001d) Fluid dynamics in airway bifurcations: III. Localized flow conditions. Inhalation Toxicol. 13: 291-305.
Matsui, H.; Randell, S. H.; Peretti, S. W.; Davis, C. W.; Boucher, R. C. (1998) Coordinated clearance of periciliary liquid and mucus from airway surfaces. J. Clin. Invest. 102: 1125-1131.
Mauderly, J. L. (1979) Effect of age on pulmonary structure and function of immature and adult animals and man. Fed. Proc. 38: 173-177.
Medinsky, M. A.; Kampcik, S. J. (1985) Pulmonary retention of [^{14}C]benzo*[a]*pyrene in rats as influenced by the amount instilled. Toxicology 35: 327-336.
Ménache, M. G.; Miller, F. J.; Raabe, O. G. (1995) Particle inhalability curves for humans and small laboratory animals. Ann. Occup. Hyg. 39: 317-328.
Mercer, T. T. (1967) On the role of particle size in the dissolution of lung burdens. Health Phys. 13: 1211-1221.
Mercer, R. R.; Russell, M. L.; Roggli, V. L.; Crapo, J. D. (1994) Cell number and distribution in human and rat airways. Am. J. Respir. Cell Mol. Biol. 10: 613-624.
Miller, F. J.; Anjilvel, S.; Ménache, M. G.; Asgharian, B.; Gerrity, T. R.. (1995) Dosimetric issues relating to particulate toxicity. Inhalation Toxicol. 7: 615-632.
Morrison, D.; Skwarski, D.; Millar, A. M.; Adams, W.; MacNee, W. (1998) A comparison of three methods of measuring ^{99m}Tc-DTPA lung clearance and their repeatability. Eur. Respir. J. 11: 1141-1146.
Morrow, P. E. (1973) Alveolar clearance of aerosols. Arch. Intern. Med. 131: 101-108.
Morrow, P. E. (1977) Clearance kinetics of inhaled particles. In: Brain, J. D.; Proctor, D. F.; Reid, L. M., eds. Respiratory defense mechanisms (in two parts), part II. New York, NY: Marcel Dekker, Inc.; pp. 491-543. (Lenfant, C., ed. Lung biology in health and disease: v. 5).
Morrow, P. E. (1986) Factors determining hygroscopic aerosol deposition in airways. Physiol. Rev. 66: 330-376.
Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.
Morrow, P. E. (1994) Mechanisms and significance of "particle overload." In: Mohr, U.; Dungworth, D. L.; Mauderly, J. L.; Oberdörster, G., eds. Toxic and carcinogenic effects of solid particles in the respiratory tract: [proceedings of the 4th international inhalation symposium]; March 1993; Hannover, Germany. Washington, DC: International Life Sciences Institute Press; pp. 17-25.
Morrow, P. E.; Yu, C. P. (1993) Models of aerosol behavior in airways and alveoli. In: Morén, F.; Dolovich, M. B.; Newhouse, M. T.; Newman, S. P., eds. Aerosols in medicine: principles, diagnosis and therapy. 2nd rev. ed. Amsterdam, The Netherlands: Elsevier; pp. 157-193.
Morrow, P. E.; Gibb, F. R.; Gazioglu, K. M. (1967) A study of particulate clearance from the human lungs. Am. Rev. Respir. Dis. 96: 1209-1221.
Musante, C. J.; Martonen, T. B. (1999) Predicted deposition patterns of ambient particulate air pollutants in children's lungs under resting conditions. In: Proceedings of the third colloquium on particulate air pollution and human health; June; Durham, NC. Irvine, CA: University of California, Air Pollution Health Effects Laboratory, p. 7-15 - 7-20.
Musante, C. J.; Martonen, T. B. (2000a) Computer simulations of particle deposition in the developing human lung. J. Air Waste Manage. Assoc. 50: 1426-1432.
Musante, C. J.; Martonen, T. B. (2000b) An extrapolation model to aid in toxicological studies of particulate air pollutants. Presented at: PM2000: particulate matter and health—the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.
Musante, C. J.; Martonen, T. B. (2000c) Particulate matter deposition in the lungs of children and adults: predictions of an age-dependent computer model. Presented at: PM2000: particulate matter and health — the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.
National Council on Radiation Protection and Measurements (NCRP). (1997) Deposition, retention and dosimetry of inhaled radioactive substances. Bethesda, MD: National Council on Radiation Protection and Measurements; report no. 125.

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

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

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

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

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

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

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

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

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.

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

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

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

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

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

Pavia, D.; Bateman, J. R. M.; Clarke, S. W. (1980) Deposition and clearance of inhaled particles. Bull. Eur. Physiopath. Respir. 16: 335-366.

Peterson, B. T.; Dickerson, K. D.; James, H. L.; Miller, E. J.; McLarty, J. W.; Holiday, D. B. (1989) Comparison of three tracers for detecting lung epithelial injury in anesthetized sheep. J. Appl. Physiol. 66: 2374-2383.

Phalen, R. F.; Oldham, M. J.; Beaucage, C. B.; Crocker, T. T.; Mortensen, J. D. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat. Rec. 212: 368-380.

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.; Holmes, A.; Evans, J. C.; Evans, N.; Evans, R. J.; Morgan, A. (1985) The distribution of dust in the rat lung following administration by inhalation and by single intratracheal instillation. Environ. Res. 36: 268-297.

Pritchard, J. N.; Jefferies, S. J.; Black, A. (1986) Sex differences in the regional deposition of inhaled particles in the 2.5-7.5 μm size range. J. Aerosol Sci. 17: 385-389.

Raabe, O. G.; Al-Bayati, M. A.; Teague, S. V.; Rasolt, A. (1988) Regional deposition of inhaled monodisperse, coarse, and fine aerosol particles in small laboratory animals. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 53-63.

Radford, E. P.; Martell, E. A. (1977) Polonium-210: lead-210 ratios as an index of residence time of insoluble particles from cigarette smoke in bronchial epithelium. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 2; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 567-581.

Rasmussen, T. R.; Andersen, A.; Pedersen, O. F. (2000) Particle deposition in the nose related to nasal cavity geometry. Rhinology 38: 102-107.

Roy, M. (1989) Lung clearance modeling on the basis of physiological and biological parameters. Health Phys. 57(suppl. 1): 255-262.

Rutland, J.; Cole, P. J. (1981) Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. Thorax 36: 654-658.

Sabaitis, C. P.; Leong, B. K. J.; Rop, D. A.; Aaron, C. S. (1999) Validation of intratracheal instillation as an alternative for aerosol inhalation toxicity testing. J. Appl. Toxicol. 19: 133-140.

Sarangapani, R.; Wexler, A. S. (2000) Modeling particle deposition in extrathoracic airways. Aerosol Sci. Technol. 32: 72-89.

Scheuch, G.; Stahlhofen, W. (1988) Particle deposition of inhaled aerosol boluses in the upper human airways. J. Aerosol Med. 1: 29-36.

Scheuch, G.; Philipson, K.; Falk, R.; Svartengren, M.; Stahlhofen, W.; Camner, P. (1995) Retention of particles inhaled in boli with and without induced bronchoconstriction. Exp. Lung Res. 21: 901-916.

Schlesinger, R. B. (1985) Clearance from the respiratory tract. Fundam. Appl. Toxicol. 5: 435-450.

Schlesinger, R. B. (1988) Biological disposition of airborne particles: basic principles and application to vehicular emissions. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 239-298.

Schlesinger, R. B. (1989) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corp.; pp. 163-192.

Schlesinger, R. B. (1995) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. 2nd ed. Washington, DC: Taylor & Francis; pp. 191-224.

Schlesinger, R. B.; Gurman, J. L.; Lippmann, M. (1982) Particle deposition within bronchial airways: comparisons using constant and cyclic inspiratory flows. Ann. Occup. Hyg. 26: 47-64.

Schlesinger, R. B.; Ben-Jebria, A.; Dahl, A. R.; Snipes, M. B.; Ultman, J. (1997) Disposition of inhaled toxicants. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press; pp. 493-550.

Schroter, R. C.; Sudlow, M. F. (1969) Flow patterns in models of the human bronchial airways. Respir. Physiol. 7: 341-55.

Segal, R. A.; Guan, X.; Shearer, M; Martonen, T. B. (2000a) Mathematical model of airflow in the lungs of children I: effects of tumor sizes and locations. J. Theor. Med. 2:199-213.

Segal, R. A.; Martonen, T. B.; Kim, C. S. (2000b) Comparison of computer simulations to total lung deposition to human subject data in healthy test subjects. J. Air Waste Manage. Assoc. 50: 1262-1268.

Segal, R. A.; Martonen, T. B.; Kim, C. S.; Shearer, M. (2002) Computer simulations of particle deposition in the lungs of chronic obstructive pulmonary disease patients. Inhalation Toxicol. 14: 705-720.

Smaldone, G. C.; Perry, R. J.; Bennett, W. D.; Messina, M. S.; Zwang, J.; Ilowite, J. (1988) Interpretation of "24 hour lung retention" in studies of mucociliary clearance. J. Aerosol Med. 1: 11-20.

Smaldone, G. C.; Foster, W. M.; Oriordan, T. G.; Messina, M. S.; Perry, R. J.; Langenback, E. G. (1993) Regional impairment of mucociliary clearance in chronic obstructive pulmonary disease. Chest 103: 1390-1396.

Snipes, M. B. (1989) Long-term retention and clearance of particles inhaled by mammalian species. CRC Crit. Rev. Toxicol. 20: 175-211.

Snipes, M. B.; Clem, M. F. (1981) Retention of microspheres in the rat lung after intratracheal instillation. Environ. Res. 24: 33-41.

Snipes, M. B.; McClellan, R. O.; Mauderly, J. L.; Wolff, R. K. (1989) Retention patterns for inhaled particles in the lung: comparisons between laboratory animals and humans for chronic exposures. Health Phys. 57(suppl. 1): 69-78.

Snipes, M. B.; James, A. C.; Jarabek, A. M. (1997) The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. Appl. Occup. Environ. Hyg. 12: 547-554.

Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G.; Philipson, K. (1986a) Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: Aerosols: formation and reactivity, proceedings of the second international aerosol conference; September; Berlin, Federal Republic of Germany. Oxford, United Kingdom: Pergamon Press; pp. 192-196.

Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G. (1986b) Measurement of lung clearance with pulses of radioactively-labelled aerosols. J. Aerosol Sci. 17: 333-336.

Stanley, P. J.; Wilson, R.; Greenstone, M. A.; Mackay, I. S.; Cole, P. J. (1985) Abnormal nasal mucociliary clearance in patients with rhinitis and its relationship to concomitant chest disease. Br. J. Dis. Chest 79: 77-82.

Stapleton, K. W.; Guentsch, E.; Hoskinson, M. K.; Finlay, W. H. (2000) On the suitability of κ-ε turbulence modeling for aerosol deposition in the mouth and throat: a comparison with experiment. J. Aerosol Sci. 31: 739-749.

Stöber, W.; Morrow, P. E.; Koch, W.; Morawietz, G. (1994) Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J. Aerosol Sci. 25: 975-1002.

Strom, K. A.; Chan, T. L.; Johnson, J. T. (1988) Pulmonary retention of inhaled submicron particles in rats: diesel exhaust exposures and lung retention model. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 645-657.

Suarez, S.; Kazantseva, M.; Bhat, M.; Costa, D.; Hickey, A. J. (2001) The influence of suspension nebulization or instillation on particle uptake by guinez pig alveolar macrophages. Inhalation Toxicol. 13: 773-788.

Subramaniam, R. P.; Richardson, R. B.; Morgan, K. T.; Guilmette, R. A.; Kimbell, J. S. (1998) Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. Inhalation Toxicol. 10: 91-120.

Subramaniam, R. P.; Asgharian, B.; Miller, F. J.; Anjilvel, S.; Freijer, J. I. (2003) Analysis of lobar differences in particle deposition in the human lung. Inhalation Toxicol. 15: 1-21.

Svartengren, K.; Lindestad, P.; Svartengren, M.; Philipson, K.; Bylin, G.; Camner, P. (1995) Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. Am. J. Respir. Crit. Care Med. 152: 32-37.

Svartengren, K.; Philipson, K.; Svartengren, M.; Anderson, M.; Camner, P. (1996a) Tracheobronchial deposition and clearance in small airways in asthmatic subjects. Eur. Respir. J. 9: 1123-1129.

Svartengren, K.; Ericsson, C. H.; Svartengren, M.; Mossberg, B.; Philipson, K.; Camner, P. (1996b) Deposition and clearance in large and small airways in chronic bronchitis. Exp. Lung Res. 22: 555-576.

Svartengren, K.; Philipson, K.; Svartengren, M.; Camner, P. (1998) Effect of adrenergic stimulation on clearance from small ciliated airways in healthy subjects. Exp. Lung Res. 24: 149-158.

Svartengren, M.; Svartengren, K.; Aghaie, F.; Philipson, K.; Camner, P. (1999) Lung deposition and extremely slow inhalations of particles. Limited effect of induced airway obstruction. Exp. Lung Res. 25: 353-366.

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

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

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

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

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

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

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

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

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

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

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

U.S. Environmental Protection Agency. (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.

Warheit, D. B.; Hartsky, M. A. (1990) Species comparisons of proximal alveolar deposition patterns of inhaled particulates. Exp. Lung Res. 16: 83-99.

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

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

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

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

Xu, G. B.; Yu, C. P. (1986) Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci. Technol. 5: 349-357.

Yeates, D. B.; Aspin, M. (1978) A mathematical description of the airways of the human lungs. Respir. Physiol. 32: 91-104.

Yeates, D. B.; Aspin, N.; Levison, H.; Jones, M. T.; Bryan, A. C. (1975) Mucociliary tracheal transport rates in man. J. Appl. Physiol. 19: 487-495.

Yeates, D. B.; Pitt, B. R.; Spektor, D. M.; Karron, G. A.; Albert, R. E. (1981) Coordination of mucociliary transport in human trachea and intrapulmonary airways. J. Appl. Physiol. 51: 1057-1064.

Yeh, H.-C.; Schum, G. M. (1980) Models of human lung airways and their application to inhaled particle deposition. Bull. Math. Biol. 42: 461-480.

Yu, G.; Zhang, Z.; Lessmann, R. (1998) Fluid flow and particle diffusion in the human upper respiratory system. Aerosol Sci. Technol. 28: 146-158.

Zhang, Z.; Martonen, T. (1997) Deposition of ultrafine aerosols in human tracheobronchial airways. Inhalation Toxicol. 9: 99-110.

Zhang, L.; Asgharian, B.; Anjilvel, S. (1997) Inertial deposition of particles in the human upper airway bifurcations. Aerosol Sci. Tech. 26: 97-110.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2000) Effects of asymmetric branch flow rates on aerosol deposition in bifurcating airways. J. Med. Eng. Technol. 24: 192-202.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2001) Effects of curved inlet tube on air flow and particle deposition in bifurcating lung models. J. Biomechanics 34: 659-669.

Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2002) Cyclic micron-size particle inhalation and deposition in a triple bifurcation lung airway model. J. Aerosol Sci. 33: 257-281.

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

7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS

7.1 INTRODUCTION

Toxicological research on airborne particulate matter (PM) during the past five years or so has focused strongly on addressing several interrelated questions, such as: (1) what characteristics (size, chemical composition, etc.) of ambient PM cause or contribute to health effects; (2) what evidence is available for elucidating potential mechanisms underlying PM health effects; (3) what susceptible subgroups are at increased risk for ambient PM health effects and what types of factors contribute to their increased susceptibility; and (4) what evidence exist that illustrates examples of interactive effects of particles and gaseous co-pollutants?

A variety of research approaches have been and continue to be used to address these questions, including studies of human volunteers exposed to PM under controlled conditions; in vivo studies of laboratory animals including nonhuman primates, dogs, and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. Similarly, a wide variety of exposure conditions and exposure concentrations/doses have been employed, including whole body and nose-only inhalation exposures to laboratory-generated PM or concentrated ambient PM, intratracheal instillation, and in vitro exposure to test materials in solution or suspension. These research approaches have been targeted mainly to test hypotheses to provide improved understanding of the role of PM in producing health effects identified by epidemiologic studies. Thus, most of the toxicological studies have been designed to address the question of biologic plausibility of epidemiologically-demonstrated effects, rather than providing dose-response quantification for experimentally-induced toxic effects. Much care should therefore be taken when attempting to extrapolate effects seen in these studies to humans under "real world" exposure conditions.

Particulate matter is a broad term that encompasses myriad physical and chemical species, some of which have been investigated in the controlled laboratory animal or human studies. However, a full discussion of all types of particles that have been studied is beyond the scope of this chapter (see Chapter 2). Thus, specific criteria were used to select topics for presentation. High priority was placed on studies that (1) elucidate health effects of ambient PM or its major

common constituents and/or (2) may contribute to enhanced understanding of PM epidemiologic study results. Diesel particulate matter (DPM) generally fits the above criteria; however, because it is described in other documents in great detail (U. S. Environmental Protection Agency, 1999; Health Effects Institute, 1995), only limited aspects (e.g., chronic animal studies, controlled human studies, and immune effects) are covered in this chapter. Particles with high inherent toxicity, such as silica, that are of concern mostly because of occupational exposure, are excluded from this chapter and are discussed in detail in other documents and reports (e.g., U.S. Environmental Protection Agency, 1996b; Gift and Faust, 1997).

Because of the sparsity of toxicological data on ambient PM at the time of the previous PM Air Quality Criteria Document or "PM AQCD" (U.S. Environmental Protection Agency, 1996a), the discussion of toxicologic effects of PM was organized there into specific chemical components of ambient PM or model "surrogate" particles (e.g., acid aerosols, metals, ultrafine particles, bioaerosols, "other particle matter"). Many of the newer toxicological studies evaluate potential toxic effects of combustion-related particles. The main reason for this extensive interest in combustion particles is that these particles, along with the secondary aerosols that they form, are typically among the most dominant components represented in the fine fraction of ambient air PM.

This chapter is organized as follows. The respiratory effects of specific components of ambient PM or surrogate particles delivered by controlled in vivo exposures of both humans and laboratory animals are discussed first (Section 7.2), followed by discussion of cardiovascular and systemic effects of in vivo PM exposure (Section 7.3). In vitro exposure studies are discussed next (Section 7.4) and are valuable in providing information on potential hazardous constituents and mechanisms of PM injury. Studies of PM effects in laboratory animal models that mimic human disease are then discussed (Section 7.5) as providing information useful for characterizing factors affecting susceptibility to PM effects. Section 7.6 assesses controlled-exposure studies evaluating health effects of mixtures of ambient PM or PM surrogates with gaseous pollutants. This organization provides the underlying data for interpretive evaluation in the final section (Section 7.7), but it may not fully convey the extensive and intricate linkages among the pulmonary, cardiac, and nervous systems, all of which may be involved individually and/or in concert in mediating PM exposure effects.

7.2 RESPIRATORY EFFECTS OF PARTICULATE MATTER IN HEALTHY HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES

This section assesses the respiratory effects of (a) controlled human exposure to various types of PM and (b) controlled laboratory animal PM exposures. Related in vitro studies using animal or human respiratory cells are discussed in Section 7.4.

The biological responses occurring in the respiratory tract following controlled PM inhalation include changes in pulmonary inflammation and systemic effects resulting from direct effects on lung tissue. The observed responses may be dependent on the physicochemical characteristics of the PM, the exposure, and the health status of the host. Many of the responses are usually seen only at the higher concentrations typical of occupational and laboratory animal exposures and not necessarily at (typically much lower) ambient particle concentrations. Moreover, there are substantial differences in the inhalability and deposition profiles of PM in humans and rodents (see Chapter 6 for details). Observed responses and dose-response relationships also are very dependent on the specific biological response being measured.

Most of the laboratory animal studies summarized here used high particulate mass concentrations administered by inhalation or by intratracheal instillation. The doses used are generally quite high when compared to ambient exposure levels, even when laboratory animal-to-human dosimetric differences are considered. Such high doses may be necessary, however, in laboratory animal studies that explore potentially toxic effects using numbers of subjects (animals) that are orders of magnitude fewer than numbers of human subjects included in most epidemiology analyses. Further research on particle dose extrapolation is thusly needed to determine species differences and to delineate the importance of exercise and other factors influencing particle deposition in humans that, together, can account for large (possibly 50-fold or more) differences in dose. Another important consideration is that healthy animals are most typically used in controlled-exposure toxicology studies, whereas epidemiologic findings often reflect ambient pollutant effects on susceptible or compromised humans (e.g., children or those with one or another chronic disease). A key question, then, is the extent to which high-dose PM exposures in healthy animals or even in acutely damaged animals exert toxic effects via similar mechanisms operating in humans in response to exposures to doses of ambient PM.

As noted earlier, data available in the 1996 PM AQCD were from studies that evaluated respiratory effects of specific components of ambient PM or surrogate particles, e.g., pure

sulfuric acid droplets. More recently, pulmonary effects of controlled exposures to ambient PM have been investigated by the use of particles collected from emission source bag filters or ambient samplers (e.g., impactors; diffusion denuders) and by the use of aerosol concentrators (e.g., Sioutas et al., 1995a,b, 2000; Gordon et al., 1998; Chang et al., 2000, Kim et al., 2000a,b). Particles from ambient air samplers are collected on filters or other media, stored, and resuspended in an aqueous medium for use in inhalation, intratracheal installation, or in vitro studies. Both ambient PM and concentrated ambient particles (CAPs) have been used to evaluate effects in normal and compromised laboratory animals and humans. Some ambient PM has been standardized as a reference material and compared to existing dust and soot standards [e.g., National Institutes of Standards and Technology (NIST)].

Particle concentrators provide a technique for exposing animals or humans by inhalation to concentrated ambient particles (CAPs) at levels higher than typical ambient PM concentrations. The development of particle concentrators has permitted the study of ambient real-world particles under controlled conditions. This strength is somewhat weakened by the inability of CAPs studies to precisely control the mass concentration and day-to-day variability in ambient particle composition. Nonetheless, these studies are invaluable in the attempt to understand the biological mechanisms responsible for the cardiopulmonary response to inhaled PM. Because the composition of concentrated ambient PM varies in both time and location, a thorough physical-chemical characterization is necessary to compare results among studies or even among exposures within studies or to link particle composition to effect.

The in vivo studies discussed here and in vitro studies discussed later have almost exclusively used PM_{10} or $PM_{2.5}$ as particle size cutoffs for studying the adverse effects of ambient PM. Studying particles in such size ranges is justified based in part on interests in evaluating the bases for existing PM_{10} and $PM_{2.5}$ standards. In addition, collection of these size fractions has been made easier by widespread availability of ambient sampling equipment for PM_{10} and $PM_{2.5}$. Unfortunately, the study of other important size fractions, such as the coarse fraction ($PM_{10-2.5}$) and $PM_{1.0}$ has been largely ignored, and only limited toxicology data are available to specifically address these potentially important particle sizes. Similarly, although organic compounds often comprise 20 to 60% of the dry fine particle mass of ambient PM (Chapter 3), little research has addressed mechanisms by which this organic fraction contributes to adverse effects associated with ambient PM exposures. The potential contribution of organics

in mutagenesis and carcinogenesis has been studied, but these extensive findings are only briefly discussed in this chapter (Section 7.4.3.2), which mainly focuses on studies aimed at evaluating the biological plausibility of epidemiologic evidence for increased cardiopulmonary morbidity and mortality being associated with exposure to ambient PM.

7.2.1 Ambient Combustion-Related and Surrogate Particulate Matter

Some new in vivo toxicology studies utilizing inhalation exposure as a technique for evaluating the respiratory effects of ambient particles in humans and laboratory animals have been conducted with CAPs and with DPM. However, the vast majority of the new in vivo exposure studies have utilized intratracheal instillation techniques. 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 the collected PM may be altered by deposition and storage 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 dose is accurate even though the particle deposition and distribution patterns differ somewhat from that of inhalation. 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 inflammation and lung injury. Tables 7-1a,b, 7-2a,b, and 7-3 summarize 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 had shown that ultrafine particles have the capacity to cause injury to cells of the respiratory tract. High

TABLE 7-1a. RESPIRATORY EFFECTS OF INHALED AMBIENT PARTICULATE MATTER IN CONTROLLED EXPOSURE STUDIES OF HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
Humans, healthy nonsmokers; 18 to 40 yr old	CAPs (Chapel Hill)	Inhalation	23.1 to 311.1 μg/m^3	0.65 μm σg = 2.35	2 h; analysis at 18 h	Increased BAL neutrophils in both bronchial and alveolar fractions. Particles were concentrated 6- to 10-fold at the inlet of the chamber.	Ghio et al. (2000a)
Humans, healthy; n=4, 19-41 yr old	CAPs (LA)	Inhalation	148-246 μg/m^3	$PM_{2.5}$	2 h	No significant changes in lung function, symptoms, S_aO_2, or Holter ECGs were observed. The maximum steady state fine particle concentration in the breathing zone was typically seven times the ambient concentration.	Gong et al. (2000)
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	73.5 to 733 μg/m^3 for Days 1-3; 29 °C, 47 and 59% RH	0.18 and 0.27 μm σg = 2.9	5 h/day for 3 days	PEF and TV increased in CAPS exposed animals. Increased protein and percent neutrophils and lymphocytes in lavage fluid after CAPS exposure. Responses were greater in SO_2-bronchitis animals. No changes in LDH. No deaths occurred. Exposures were to 30-40 times greater PM concentrations than found in ambient air.	Clarke et al. (1999) Saldiva et al. (2002)
Mongrel dogs, some with balloon occluded LAD coronary artery n = 14	CAPs (Boston)	Inhalation via tracheostomy	69-828 μg/m^3	0.23 to 0.34 μm σg = 0.2 to 2.9	6 h/day × 3 days	Decreased respiratory rate and increased lavage fluid neutrophils in normal dogs. Study utilized Harvard ambient particle concentrator. Ambient particles concentrated by approximately 30-fold.	Godleski et al. (2000)
Rats, male F 344 Hamsters, male, 8-mo-old Bi TO-2	CAPs (NY)	Inhalation	132 to 919 μg/m^3	0.2 to 1.2 μm σg = 0.2 to 3.9	1 × 3 h or 3 × 6 h	No inflammatory responses, no cell damage responses, no PFT changes. The PM mean concentration factor (gravimetric) was 19.5 ± 18.6.	Gordon et al. (2000)
Rats, male, 90 to 100-day-old S-D, with or without SO_2-induced bronchitis	CAPs (RTP)	Inhalation	650 μg/m^3		6 h/day × 2-3 days	No significant changes in healthy rats; increased BALF protein and neutrophil influx in bronchitic rats; responses were variable between exposure regimens.	Kodavanti et al. (2000a)
Rats, male F344	CAPs (NY)	Inhalation	100-350 μg/m^3 (mean 225μg/m^3)	0.4 μm σg = 2.5	3 h	Basal levels of superoxide ($\bullet O_2^-$) reduced by 90% 72 h postexposure; zymosan-stimulated O_2^- formation increased by > 150% after 24 h; basal level H_2O_2 production by PAM depressed 90% 3 h following exposure and remained 60% below levels at least 24 h; zymosan-stimulated H_2O_2 unaffected.	Zelikoff et al. (2003)

[a]PEF = Peak expiratory flow
TV = tidal volume
LDH = lactic dehydrogenase
S_aO_2 = arterial oxygen saturation

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-1b. RESPIRATORY EFFECTS OF INSTILLED AMBIENT PARTICULATE MATTER IN LABORATORY ANIMALS AND HUMAN SUBJECTS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
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 produced by particles collected during steel mill operation was greater than for during period of mill closure.	Dye et al. (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)
Rats, Wis (HAN strain)	Ambient PM Edinburgh, CB, CB Ultrafine (UCB)	Intratracheal instillation	50-125 µg in .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)
Rats, S-D	DEP	Intratracheal instillation	500 µg in 0.5 ml saline	N/A	3 times/wk, 2 wk	Decreased concentration of lavage ascorbate. Urate and glutathione concentrations unchanged; elevated MIP-2 and TNF; total cell count increased; lavage protein and LDH increased; increased total lavage iron concentration.	Ghio et al. (2000b)
Humans, healthy nonsmokers; 21 M, 3 F; 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 produced by particles collected during steel mill operation was greater than for during period of mill closure.	Ghio and Devlin (2001)

[a]PEF = Peak expiratory flow
TV = tidal volume
LDH = lactic dehydrogenase
S_aO_2 = arterial oxygen saturation

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-2a. RESPIRATORY EFFECTS OF INSTILLED COMPLEX COMBUSTION-RELATED PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
Hamsters, Syrian golden, male, 90-125 g	Kuwaiti oil fire particles; urban particles from St. Louis, MO	Intratracheal instillation	0.15, 0.75, and 3.75 mg/100 g	Oil fire particles: < 3.5 µm, 10 days of 24-h samples	Sacrificed 1 and 7 days postinstillation	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, 28-32 g	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 post-treatment, 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, S-D, 60 days old	ROFA	Intratracheal instillation	8.33 mg/mL 0.3 mL/rat	1.95 µm	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	24h	Increased neutrophilic inflammation was inhibited by DMTU treatment, indicating role reactive oxygen species.	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-2a (cont'd). RESPIRATORY EFFECTS OF INSTILLED COMPLEX COMBUSTION-RELATED PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
Rats, male, S-D, 5-day-old	lo-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 R2: 2.03 µm	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	#6 ROFA, lo-S	Intratracheal instillation	60 µg in 50 µL (dose 3 mg/kg)	< 2.5	Analysis at 1, 3, 8, 15 days after instillation	ROFA caused increases in eosinophils, IL-4 and IL-5 and airway responsiveness in ovalbumin-sensitized and challenged mice. Increased BAL protein and LDH at 1 and 3 days but not at 15 days postexposure. Combined OVA and ROFA challenge increased all damage markers and enhanced allergen sensitization. Increased methacholine response after ROFA.	Gavett et al. (1999)
Rats, male, S-D	ROFA	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. (1998a)
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. (2000c)
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, male, S-D and F-344 (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 µm σg = 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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-2a (cont'd). RESPIRATORY EFFECTS OF INSTILLED COMPLEX COMBUSTION-RELATED PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
Rats, male, S-D, WIS, and F-344 (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 µm σg = 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 σg = 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	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)
Rats, male, S-D 60-day-old treated with MCT (60 mg/kg)	ROFA	Intratracheal instillation	0, 0.83, 3.3 mg/kg	1.95 µm σg = 2.14	24-96 h	IT rats showed inflammatory responses (IL-6, MIP-2 genes upregulated). 58% of rats exposed to ROFA died within 96 h.	Kodavanti et al. (1999)
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; postinstillation analysis at 6 or 24 h	Increased BALF protein and LDH alveolitis with macrophage accumulation in alveoli; increased neutrophils in BAL. Increased pulmonary protein leakage and inflammation in SH rats. Effects of metal constituents of ROFA were strain specific; vanadium caused pulmonary injury only in WKY rats; nickel was toxic in both SH and WKY rats.	Kodavanti et al. (2001)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-2a (cont'd). RESPIRATORY EFFECTS OF INSTILLED COMPLEX COMBUSTION-RELATED PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
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 saline	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 $\sigma_g = 2.14$	3 or 24 h	Inflammatory and stress responses were upregulated; the numbers of genes upregulated were correlated with metal type and ROFA	Nadadur et al. (2000); Nadadur and Kodavanti (2002)
Rats, male, S-D, 60-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)
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	Dose: IT 0, 0.25, 1.0, and 2.5 mg/rat	1.95 µm	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]CFA = Coal fly ash
CMP = Copper smelter dust
WC = Tungsten carbide
MCT = Monocrotaline
DOFA = Fly ash from a domestic oil-burning furnace
ROFA = Residual oil fly ash
$Fe_2(SO_4)$ = Iron sulfate
VSO_4 = Vanadium sulfate
$NiSO_4$ = Nickel sulfate
LoS = low sulfur
OVA = Ovalbumin

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-2b. RESPIRATORY EFFECTS OF INHALED COMPLEX COMBUSTION-RELATED PARTICULATE MATTER IN COMPROMISED LABORATORY ANIMAL MODELS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles/Comments	Reference
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)
Mice, BALB/C, 2-day-old, sensitized to ovalbumin (OVA)	Aerosolized ROFA leachate	Nose-only inhalation	50 mg/mL	N/A	30 min	Increased airway response to methylcholine and to OVA in ROFA exposed mice; increased airway inflammation also.	Hamada et al. (1999)
Rats, S-D, 250 g MCT	ROFA	Inhalation	580 ± 110 µg/m^3	2.06 µm σg = 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 60-day-old treated with MCT (60 mg/kg)	ROFA	Nose-only inhalation	15 mg/m^3	1.95 µm σg = 2.14	6 h/day for 3 days analysis at 0 or 18 h	No mortality occurred by inhalation. ROFA exacerbated lung lesions (edema, inflammation, alveolar thickening) and gene expression in MCT rats. Rats showed inflammatory responses (IL-6, MIP-2 genes upregulated).	Kodavanti et al. (1999)
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 Acctylcholine 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)

[a]CFA = Coal fly ash
CMP = Copper smelter dust
WC = Tungsten carbide
MCT = Monocrotaline
DOFA = Fly ash from a domestic oil-burning furnace
ROFA = Residual oil fly ash

$Fe_2(SO_4)$ = Iron sulfate
VSO_4 = Vanadium sulfate
$NiSO_4$ = Nickel sulfate
LoS = low sulfur
OVA = Ovalbumin

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-3. RESPIRATORY EFFECTS OF SURROGATE PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Inhalation							
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 half-times retarded (males).	Creutzenberg et al. (1998)
Mice, C57Bl/6J	PTFE TiO_2	Inhalation	PTFE: 1.25, 2.5, or 5×10^5 particles/cc TiO_2-F: 10 mg/m^3 NiO: 5 mg/m^3 Ni_3S_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/cm^3	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/cm^3	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-3 (cont'd). RESPIRATORY EFFECTS OF SURROGATE PARTICULATE MATTER IN LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle[a]	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Inhalation (cont'd)							
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)
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
Instillation							
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 neutrophilic inflammation. Carbon black and DEP translocated to interstitum and lymph nodes by 12 weeks.	Murphy et al. (1998)

[a]PTFE = polytetrafluoroethylene
TiO_2 = titanium oxide
SiO_2 = silicon dioxide

DRAFT-DO NOT QUOTE OR CITE

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 $\mu g/m^3$, freshly generated insoluble ultrafine PTFE fume particles can be severely toxic to the lung. However, it is not clear as to what roles in the observed effects may have been played by fume gases which adhered to the particles. Newer data from controlled exposures have demonstrated that particle composition, in addition to particle size, may be responsible for the adverse health effects associated with ambient PM exposures.

Toxicological studies of other types of PM species were also discussed in the previous criteria document (U.S. Environmental Protection Agency, 1996a). These studies included exposures to fly ash, volcanic ash, coal dust, carbon black, and miscellaneous other particles, either alone or in mixture. Some of the particles discussed were considered to be models of "respirable low toxicity particles" and were used in instillation studies to delineate nonspecific particle effects from effects of known toxicants. A number of studies on "other PM" examined effects of up to 50,000 $\mu g/m^3$ of respirable particles with inherently low toxicity. Although there was no mortality, some mild pulmonary function changes after exposure to 5,000 to 10,000 $\mu g/m^3$ of inert particles were observed in rats and guinea pigs. Lung morphology studies revealed focal inflammatory responses, some epithelial hyperplasia, and fibrotic responses after exposure to > 5,000 $\mu g/m^3$. Changes in macrophage clearance after exposure to > 10,000 $\mu g/m^3$ were equivocal (no host defense effects). In studies of mixtures of particles and other pollutants, effects varied depending on the toxicity of the associated pollutant. In humans, co-exposure to carbon particles appeared to increase responses to formaldehyde but not to acid aerosol. None of the "other" particles mentioned above are present in ambient air in more than trace quantities. Thus, it was concluded that the relevance of any of these studies to standard setting for ambient PM may be extremely limited (see also Chapter 6, Section 4, *Particle Overload* in this draft document).

Newer studies, on the other hand, appear to provide evidence of likely greater relevance to understanding ambient PM exposure effects and underlying mechanisms.

7.2.1.1 Ambient Particulate Matter

New studies that examined the acute effects of intratracheal instillation of ambient PM obtained from specific ambient locations have shown clearly that PM can cause lung inflammation and injury.

Costa and Dreher (1997) showed that instillation of relatively high concentrations of PM samples from three emission sources (two oil and one coal fly ash) and four ambient airsheds (St. Louis, MO; Washington, DC; Dusseldorf, Germany; and Ottawa, Canada) resulted in increases in lung polymorphonuclear leucocytes (PMNs) and eosinophils in rats 24 h after instillation. Biomarkers of permeability (total protein and albumin) and cellular injury, lactic dehydrogenase (LDH), also were increased. Animals were dosed with (1) an equal dose by mass (nominal 2.5 mg/rat) of each PM mixture or (2) normalization of each PM mass to a metal content of 46 mg/dose and 35.5 μg of total metals (Cu, Fe, V, Zn) for the ambient PM and ROFA comparison. This study demonstrated that the lung dose of bioavailable transition metal, not instilled PM mass, was the primary determinant of the acute inflammatory response.

Kennedy et al. (1998) reported a similar dose-dependent inflammation (i.e., increase in protein and PMN in lavage fluid, proliferation of bronchiolar epithelium, and intraalveolar hemorrhage) in rats instilled with water-extracted particles (TSP) collected in Provo, UT. The particulate mixture was composed of 1.0 mg/g Zn, 0.04 mg/g Ni, 2.2 mg/g Fe, 0.01 mg/g Vn, 1.4 mg/g Cu, 1.7 mg/g Pb, and 78 mg/g $SO_4^=$ in 500 mL saline solution. This study also indicated that the metal constituent, in this case PM-associated Cu, was a plausible cause of the outcome based on IL-8 secretion and enhanced activation of the transcription factor NF-kB in cultured epithelium.

Further toxicological studies of ambient PM collected around Provo, UT (Utah Valley) in the late 1980s are particularly interesting (Ghio and Devlin, 2001; Dye et al., 2001; Wu et al., 2001; Soukup et al., 2000; Frampton et al., 1999). Epidemiologic studies by Pope (1989, 1991) had shown that exposures to PM_{10} during closure of an open-hearth steel mill over a 13-mo period beginning in 1987 were associated with reductions in several health endpoints, e.g., hospital admissions for respiratory diseases, as discussed in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Ambient PM was collected near the steel mill during the winter of 1986 (before closure), 1987 (during closure), and again in 1988 (after plant reopening). The fibrous glass hi-vol filters were stored, folded PM-side inward, in plastic

sleeves at room temperature and humidity (Dye et al., 2001). A description of the in vivo toxicological studies follows; the in vitro studies are discussed in Section 7.5.2.1.

Ghio and Devlin (2001) investigated the biologic effect of PM from the Utah Valley to determine if the biological responses mirrored the epidemiologic findings, with greater injury occurring after exposure to an equal mass of particles from those years in which the mill was in operation. Aqueous extracts of the filters collected prior to closure of the steel mill, during the closure and after its reopening, were instilled through a bronchoscope into the lungs of nonsmoking human volunteers. Twenty-four hours later, the same subsegment was lavaged. Exposure to aqueous extracts of PM collected before closure and after reopening of the steel mill provoked a greater inflammatory response than PM extract acquired during the plant shutdown. These results indicate that the pulmonary effects observed after experimental exposure of humans to the Utah Valley PM can be correlated with health outcomes observed in epidemiologic studies of the same material under normal exposure conditions.

Dye et al. (2001) similarly examined the relationship between Utah Valley ambient PM and respiratory health effects but in laboratory animals. Sprague-Dawley rats were intratracheally instilled with equivalent masses of aqueous extracts from filters originally collected during the winter before, during, and after closure of the steel mill. Twenty-four hours after instillation, rats exposed to extracts of particles collected when the plant was open developed significant pulmonary injury and neutrophilic inflammation. Additionally, 50% of rats exposed to these extracts had increased airway responsiveness to acetylcholine, compared to 17 and 25% of rats exposed to saline or the extracts of particles collected when the plant was closed. By 96 hr, these effects were largely resolved except for increases in lung lavage fluid neutrophils and lymphocytes in rats exposed to PM extracts from prior to the plant closing. Analogous effects were observed with lung histologic assessment. Extract analysis demonstrated that nearly 70% of the mass in all three extracts appeared to be sodium-based salts derived from the glass filter matrix. Extracts of particles collected when the plant was open contained more sulfate, cationic salts (i.e., calcium, potassium, magnesium), and certain metals (i.e., copper, zinc, iron, lead, strontium, arsenic, manganese, nickel). Although total metal content was ≈1% of the extracts by mass, the greater quantity detected in the extracts of particles collected when the plant was open suggests that metals may be important determinants of the observed pulmonary toxicity. The authors concluded that the pulmonary effects induced in rats

by exposure to aqueous extracts of local ambient PM filters were in good accord with the epidemiologic reports of adverse respiratory health effects in Utah Valley residents.

Molinelli et al. (2002) exposed human airway epithelial cell line (BEAS-2B) cultures for 24 h to an aqueous extract of PM collected in the Utah Valley. A portion of the extract was treated with Chelex, an agent that removes transition metals from solution. Cells incubated with the untreated extract showed a significant concentration-dependent increase in the inflammatory mediator interleukin-8 (IL-8) when compared to the control cells. However, cells incubated with Chelex-treated extract produced no change (relative to control) in IL-8. They exposed rats in vivo for 24 h to the same treatments as the cells and found significant increases in lactate dehydrogenase (LDH) and total protein in the rats exposed to the untreated extract and to the Chelex-treated extract with metals added back to achieve original concentrations. There was an attenuation of the observed LDH and total protein increases in the rats instilled with the Chelex-treated extract. The authors concluded that removal of metal cations attenuates cellular responses to the aqueous extract and suggest a role for transition metal involvement in PM-associated increases in morbidity and mortality.

In parallel work on potential importance of metals in mediating ambient PM effects, Kodavanti et al. (2002) examined the role of zinc in PM-induced health effects in several different animal models. Male Sprague-Dawley rats were instilled IT with an oil combustion emission PM (EPM) in saline (0.0, 0.8, 3.3, or 8.3 mg/kg); and, in order to examine the potential role of EPM leachable zinc, additional rats were instilled with either saline, whole EPM suspension, the saline leachable fraction of EPM, the particulate fraction of EPM (8.3 mg/kg, soluble Zn = 14.5 ug/mg EPM), or $ZnSO_4$ (0.0, 33.0, or 66.0 ug/kg Zn). Three rat strains of differing PM susceptibility (male SD, normotensive Wistar-Kyoto (WKY), and spontaneously hypertensive (SH) rats (90 days old)) were exposed nose-only to either filtered air or EPM (2, 5, or 10 mg/m^3 for 6 h/day x 4 days/week x 1 week; or 10 mg/m^3 for 6 h/day x 1 day/week for 1, 4, or 16 weeks) and assessed at 2 days postexposure. Intratracheal exposures to whole EPM suspensions were associated with a dose-dependent increase in protein/albumin permeability and neutrophilic inflammation. Pulmonary protein/albumin leakage and neutrophilic inflammation caused by the leachable fraction of EPM and $ZnSO_4$ were comparable to the effects of the whole suspension. However, protein/albumin leakage was not associated with the particulate fraction, although significant neutrophilic inflammation did occur following instillation. With EPM nose-

only inhalation, acute exposures (10 mg/m^3 only) for 4 days resulted in small increases in bronchoalveolar lavage fluid (BALF) protein and n-acetyl glucosaminidase activities (approximately 50% above control). Unlike IT exposures, no neutrophilic influx was detectable in BALF from any of the inhalation groups. The only major effect of acute and long-term EPM inhalation was a dose- and time-dependent increase in alveolar macrophages (AM) regardless of the rat strain. Histological evidence also showed dose- and time-dependent accumulations of particle-loaded AM. Particles were also evident in interstitial spaces, and in the lung-associated lymph nodes following the inhalation exposures (SH > WKY= SD). There were strain-related differences in peripheral white blood cell counts and plasma fibrinogen with no major EPM inhalation effect. The authors attributed the critical differences in pulmonary responsiveness to EPM between IT and inhalation exposures to the dose of bioavailable zinc. EPM IT exposures, but not acute and long-term inhalation of up to 10 mg/m^3, caused neutrophilic inflammation.

Also of interest are some other new instillation study results. For example, Li et al. (1996, 1997) reported that instillation of ambient PM_{10} collected in Edinburgh, Scotland, also caused pulmonary injury and inflammation in rats. In addition, Brain et al. (1998) examined the effects of instillation of particles that resulted from the Kuwaiti oil fires in 1991 compared to effects of urban PM collected in St. Louis (NIST SRM 1648, collected in a bag house in the early 1980s) and showed that, on an equal mass basis, the acute toxicity of the Kuwaiti oil fire particles was similar to that of urban particles collected in the United States.

The fact that instillation of ambient PM collected from different geographical areas and from a variety of emission sources consistently caused pulmonary inflammation and injury tends to corroborate epidemiologic studies that report increased PM-associated respiratory effects in populations living in many different geographical areas and climates. On the other hand, there is a potential that more "realistic" doses of metals may activate cells and signaling pathways in a manner that are not observed at doses that are magnitudes greater than present in ambient air, such that these mechanisms may be overwhelmed. Thus, high-dose instillation studies may produce different effects on the lung than inhalation exposures at more relevant concentrations.

With regard to inhalation studies more directly mimicking ambient exposures, Ghio et al. (2000a) exposed 38 healthy volunteers exercising intermittently at moderate levels of exertion for 2 h to either filtered air or particles concentrated from the air in Chapel Hill, NC (23 to 311 μg/m^2). Analysis of cells and fluid obtained 18 h after exposure showed a mild increase in

neutrophils in the bronchial and alveolar fractions of bronchoalveolar lavage (BAL) in subjects exposed to the highest quartile concentration of concentrated PM (mean of 206.7 $\mu g/m^3$). Lavage protein did not increase, and there were no other indicators of pulmonary injury. No respiratory symptoms or decrements in pulmonary function were found after exposure to CAPs. The 38 human volunteers reported on by Ghio et al. (2000a) were also examined for changes in host defense and immune parameters in BAL and blood (Harder et al., 2001). There were no changes in the number of lymphocytes or macrophages, subcategories of lymphocytes (according to surface marker analysis by flow cytometry), cytokines IL-6 and IL-8, or macrophage phagocytosis. Similarly, there was no effect of concentrated ambient PM exposure on lymphocyte subsets in blood. Thus, a mild inflammatory response to concentrated ambient PM was not accompanied by an effect on immune defenses as determined by lymphocyte or macrophage effects. The increase in neutrophils may represent an adaptive response of the lung to particles, although the presence of activated neutrophils may release biochemical mediators which produce lung injury. Whether this mild inflammatory increase in neutrophils constitutes a biologically significant injury to the lung is an ongoing controversial issue.

Other human inhalation studies with CAPs are limited by the small numbers of subjects studied. Petrovic et al. (1999) exposed four healthy volunteers (aged 18 to 40) under resting conditions to filtered air and 3 concentrations of concentrated ambient PM (23 to 124 $\mu g/m^3$) for 2 hours using a face mask. The exposure was followed by 30 minutes of exercise. No cellular signs of inflammation were observed in induced sputum samples collected at 2 or 24 hours after exposure. There was a trend toward an increase in nasal lavage neutrophils although no statistical significance was presented. The only statistically significant change in pulmonary function was a 6.4% decrease in thoracic gas volume after exposure to 124 $\mu g/m^3$ PM versus a 5.6% increase after air. A similar, small pilot study has been reported (Gong et al., 2000) in which no changes in pulmonary function or symptoms were observed in four subjects aged 19 to 41 after a 2 hour exposure to air or mean concentrations of 148 to 246 $\mu g/m^3$ concentrated ambient PM in Los Angeles, CA. Both of these laboratories are currently expanding on these preliminary findings, but no additional data are available at this time.

Saldiva et al. (2002) studied the effects on the lungs of CAPs from Boston. The study was designed (1) to determine whether short-term exposures to CAPs cause pulmonary inflammation in normal rats and rats with chronic bronchitis (CB); (2) to identify the site within the lung

parenchyma where CAPs-induced inflammation occurs; and (3) to characterize the component(s) of CAPs significantly associated with development of the inflammatory reaction. Four groups of animals were studied: (1) air treated, filtered air exposed (air-sham); (2) sulfur dioxide treated (CB), filtered air exposed (CB-sham); (3) air treated, CAPs exposed (air-CAPs); and (4) sulfur dioxide treated, CAPs exposed (CB-CAPs). Chronic bronchitis and normal rats were exposed by inhalation either to filtered air or CAPs during 3 consecutive days (5 hours/day). CAPs (as a binary exposure term) and CAPs mass (in regression correlations) induced a significant increase in bronchoalveolar lavage (BAL) neutrophils and in normal and CB animals. Numerical density of neutrophils (Nn) in the lung tissue significantly increased with CAPs in normal animals only. Greater Nn was observed in central, compared with peripheral, regions of the lung. A significant dose-dependent association was found between CAPs components and BAL neutrophils or lymphocytes, but only vanadium and bromine concentrations had significant associations with both BAL neutrophils and Nn in CAPs-exposed groups analyzed together. The authors concluded that (a) short-term exposures to CAPs from Boston induce a significant inflammatory reaction in rat lungs and (b) the reaction is influenced by particle composition.

7.2.1.2 Diesel Particulate Matter

Other controlled human exposures of ambient PM that may be relevant to this discussion were the DPM studies previously examined in detail in separate assessment documents (U.S. Environmental Protection Agency, 2000; Health Effects Institute, 1995). Briefly, the data from work shift studies suggest that the principle noncancer human hazard from exposure to diesel exhaust (DE) includes increased acute sensory and respiratory symptoms (e.g., cough, phlegm, chest tightness, wheezing) that are more sensitive indicators of possible health risks from exposure to DE than pulmonary function decrements. Immunological changes also have been demonstrated under short-term exposure scenarios to either DE or diesel particulate (DPM), and the evidence indicates that these immunological effects are caused by both the non-extractable carbon core and the adsorbed organic fraction of the diesel particle. While noncancer effects from long-term exposure to a high concentration of DPM in several laboratory animal species include pulmonary histopathology and chronic inflammation, noncancer effects in humans from long-term chronic exposure to DPM are not evident. The mode of action of DPM is not completely understood but the effects on the upper respiratory tract, observed in acute studies,

suggest a non-inflammatory irritant response while the effects on the lung, observed in chronic studies, indicate an underlying inflammatory response. Available data suggest that the carbonaceous core of the diesel particle, or metabolites of metal components of the particle, are possible causative agents for the noncancer lung effects which are mediated, at least in part, by a progressive impairment of alveolar macrophage function. The noncancer lung effects occur in response to DPM in several species and occur in rats at doses lower than those inducing particle overload.

Diesel particulate matter, therefore, can be relevant to the urban environment, particularly in urban micro-environments with heavy diesel engine traffic. The findings of controlled-exposure studies of DPM are discussed both here and in Section 7.5.3 (Particulate Matter Effects on Allergic Hosts).

Pulmonary function and inflammatory markers (as assayed in induced sputum samples or BAL) have been studied in human subjects exposed to either resuspended or freshly generated and diluted DPM. In a controlled human study, Sandstrom and colleagues (Rudell et al., 1994) exposed eight healthy subjects in an exposure chamber to diluted exhaust from a diesel engine for 1 h with intermittent exercise. Dilution of the DE was controlled to provide a median NO_2 level of approximately 1.6 ppm. Median particle number was 4.3×10^6 /cm^3, and median levels of NO and CO were 3.7 and 27 ppm, respectively (particle size and mass concentration were not provided). There were no effects on spirometry or on airway closing volume. Five of eight subjects experienced unpleasant smell, eye irritation, and nasal irritation during exposure. BAL was performed 18 hours after exposure and was compared with a control BAL performed 3 weeks prior to exposure. There was no control air exposure. Small yet statistically significant reductions were seen in BAL mast cells, AM phagocytic function, and lymphocyte CD4 to CD8+ cell ratios. A small increase in neutrophils was also observed. These findings suggest that DE may induce mild airway inflammation in the absence of spirometric changes. Although this early study provided important information on the effect of DE exposure in humans, only one exposure level was used, the number of subjects was low, and a limited range of endpoints was reported. Several follow-up studies have been done by the same and other investigators.

Rudell et al. (1996) later exposed 12 healthy volunteers to DE for 1 h in an exposure chamber. Light work on a bicycle ergometer was performed during exposure. Random, double-blinded exposures included air, DE, or DE with particle numbers reduced 46% by a particle trap.

The engine used was a new Volvo model 1990, a six-cylinder direct-injection turbocharged diesel with an intercooler, which was run at a steady speed of 900 rpm during the exposures. It is difficult to compare this study with others, because neither exhaust dilution ratios nor particle concentrations were reported. Concentrations of 27-30 ppm CO and of 2.6-2.7 ppm NO, however, suggested DPM concentrations may have equaled several mg/m^3. The most prominent symptoms during exposure were irritation of the eyes and nose, accompanied by an unpleasant smell. Both airway resistance and specific airway resistance increased significantly during the exposures. Despite the 46% reduction in particle numbers by the trap, effects on symptoms and lung function were not significantly reduced.

A follow-up study on the usefulness of a particle trap confirmed the lack of effect of the filter on DE-induced symptoms (Rudell et al., 1999). In this study, 10 healthy volunteers also underwent BAL 24 hours after exposure. Exposure to DE produced inflammatory changes in BAL, as evidenced by increases in neutrophils and decreases in macrophage phagocytic function in vitro. A 50% reduction in the particle number concentration by the particle trap did not alter these BAL cellular changes. Salvi et al. (1999) exposed healthy human subjects to diluted DE (DPM = 300 $\mu g/m^3$) for 1 h with intermittent exercise. As reported in the studies by Rudell and Sandstrom (Rudell et al., 1990, 1996, 1999; Blomberg et al., 1998; Salvi et al., 1999) significant increases in neutrophils and B lymphocytes, as well as histamine and fibronectin in airway lavage fluid, were not accompanied by decrements in pulmonary function. Bronchial biopsies obtained 6 h after DE exposure showed a significant increase in neutrophils, mast cells, and CD4+ and CD8+ T lymphocytes, along with upregulation of the endothelial adhesion molecules ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) and increases in the number of leukocyte function-associated antigen-1 (LFA-1+) in the bronchial tissue. Importantly, extra-pulmonary effects were observed in these subjects. Significant increases in neutrophils and platelets were found in peripheral blood following exposure to DE.

Several DE toxicity studies cited in the EPA Health Effects of Diesel Exhaust Health Assessment (2000) compared the effects of whole, unfiltered exhaust to those produced by the gaseous components of the exhaust. Heinrich et al. (1982) compared the toxic effects in hamsters and rats exposed to whole and filtered DE. Exposures were to 3.9 mg/m^3 for 7 to 8 hrs/day and 5 days/week. Rats exposed for 24 mo to either whole or filtered exhaust exhibited no significant changes in respiratory frequency, respiratory minute volume, compliance or

resistance, as measured by whole body plethysmography, and heart rate. In the hamsters, histological changes (adenomatous proliferations) were seen in the lungs of animals exposed to either whole or filtered exhaust; however, in all groups exposed to the whole exhaust, the number of hamsters exhibiting such lesions was significantly higher than for the corresponding groups exposed to filtered exhaust or clean air. Severity of the lesions was not reported.

In a second study Heinrich et al. (1986) and Stöber (1986) compared the toxic effects of whole and filtered DE on hamsters, rats, and mice. The test animals (96 per test group) were exposed to 4.24 mg/m^3 DPM for 19 hrs/day, 5 days/week for 120 (hamsters and mice) or 140 (rats) weeks. Body weights of hamsters were unaffected by either exposure; whereas those of rats and mice were reduced by the whole exhaust but not by the filtered exhaust. Exposure-related higher mortality rates occurred in mice after 2 years of exposure to whole exhaust. After 1 year of exposure to whole exhaust, hamsters exhibited increased lung weights, a significant increase in airway resistance, and a nonsignificant reduction in lung compliance. For the same time period, rats exhibited increased lung weights, a significant decrease in dynamic lung compliance, and a significant increase in airway resistance. Test animals exposed to filtered exhaust did not exhibit these effects. In hamsters, filtered exhaust caused no significant histopathological effects in the lung; but whole exhaust caused thickened alveolar septa, bronchiolo-alveolar hyperplasia, and emphysematous lesions. In mice, whole exhaust, but not filtered exhaust, caused multifocal bronchiolo-alveolar hyperplasia, multifocal alveolar lipoproteinosis, and multifocal interstitial fibrosis. In rats, there were no significant morphological changes in the lungs following exposure to filtered exhaust. In rats exposed to whole exhaust, there were severe inflammatory changes in the lungs, thickened alveolar septa, foci of macrophages, crystals of cholesterol, and hyperplastic and metaplastic lesions. Biochemical studies of lung lavage fluids of hamsters and mice indicated that exposure to filtered exhaust caused fewer changes than did exposure to whole exhaust. The latter produced significant increases in lactate dehydrogenase, alkaline phosphatase, glucose-6-phosphate dehydrogenase (G6PDH), total protein, protease (pH 5.1), and collagen. The filtered exhaust had a slight but nonsignificant effect on G6PDH, total protein, and collagen. Similarly, cytological studies showed that while the filtered exhaust had no effect on differential cell counts, the whole exhaust resulted in an increase in leukocytes (161 ± 43.3/μL versus 55.7 ± 12.8/μL controls), a decrease in AMs (30.0 ± 12.5 versus 51.3 ± 12.5/μL in the controls), and an

increase in granulocytes (125 ± 39.7 versus 1.23 ± 1.14/μL in the controls). The differences were significant for each cell type. There was also a small increase in lymphocytes (5.81 ± 4.72 versus 3.01 ± 1.23 μL in the controls).

Iwai et al. (1986) exposed rats (24 per group) to whole or filtered DE 8 h/day, 7 days/week for 24 mo. The whole exhaust was diluted to a concentration of 4.9 or 1.6 mg/m^3 DPM. Body weights in the whole exhaust group began to decrease after 6 mo and in both exposed groups after 18 mo. Lung-to-body weight ratios of the rats exposed to the whole exhaust showed a significant increase ($p < 0.01$) after 12 mo in comparison with control values. Spleen-to-body weight ratios of both exposed groups were higher than control values after 24 mo. After 6 mo of exposure to whole exhaust, DPM accumulated in AMs, and Type II cell hyperplasia was observed. After 2 years of exposure, the alveolar walls had become fibrotic with mast cell infiltration and epithelial hyperplasia. In rats exposed to filtered exhaust, after 2 years there were only minimal histologic changes in the lungs, with slight hyperplasia and stratification of bronchiolar epithelium and infiltration of atypical lymphocytic cells in the spleen.

Brightwell et al. (1986) evaluated the toxic effects of whole and filtered DE on rats and hamsters. Three exhaust dilutions were tested, producing concentrations of 0.7, 2.2, and 6.6 mg/m^3 DPM. The test animals (144 rats and 312 hamsters per exposure group) were exposed for five 16-h periods per week for 2 years. The four exhaust types were gasoline, gasoline catalyst, diesel, and filtered diesel. The results presented were limited to statistically significant differences between exhaust-exposed and control animals. The inference from the discussion section of the paper was that there was a minimum of toxicity in the animals exposed to filtered DE: "It is clear from the results presented that statistically significant differences between exhaust-exposed and control animals are almost exclusively limited to animals exposed to either gasoline or unfiltered diesel exhaust."

Heinrich et al. (1995) exposed female NMRI and C57BL/6N mice to a DE dilution that resulted in a DPM concentration of 4.5 mg/m^3 and to the same dilution after filtering to remove the particles. This study is focused on the carcinogenic effects of DPM exposure, and inadequate information was presented to compare noncancer effects in filtered versus unfiltered exhaust.

A comparison of the toxic responses in laboratory animals exposed to whole exhaust or filtered exhaust containing no particles demonstrates across studies that, when the exhaust is

sufficiently diluted to limit the concentrations of gaseous irritants (NO_2 and SO_2), irritant vapors (aldehydes), CO, or other systemic toxicants, the diesel particles are the prime etiologic agents of noncancer health effects, although additivity or synergism with the gases cannot be ruled out. These toxic responses are both functional and pathological and represent a cascading sequelae of lung pathology based on concentration and species. The diesel particles plus gas exposures produced biochemical and cytological changes in the lung that are much more prominent than those evoked by the gas phase alone. Such marked differences between whole and filtered DE are also evident from general toxicological indices, such as decreases in body weight and increases in lung weights, pulmonary function measurements, and pulmonary histopathology (e.g., proliferative changes in Type II cells and respiratory bronchiolar epithelium fibrosis). Hamsters, under equivalent exposure regimens, have lower levels of retained DPM in their lungs than rats and mice and, consequently, less pulmonary function impairment and pulmonary pathology. These differences may result from lower DPM inspiration and deposition during exposure, greater DPM clearance, or lung tissue less susceptible to the cytotoxicity of deposited DPM.

In a follow-up investigation of potential mechanisms underlying the DE-induced airway leukocyte infiltration, Salvi et al. (2000) exposed healthy human volunteers to diluted DE on two separate occasions for 1 h each, in an exposure chamber. Fiber-optic bronchoscopy was performed 6 h after each exposure to obtain endobronchial biopsies and bronchial wash (BW) cells. These workers observed that diesel exhaust (DE) exposure enhanced gene transcription of interleukin-8 (IL-8) in the bronchial tissue and BW cells and increased growth-regulated oncogene-α protein expression and IL-8 in the bronchial epithelium; there was also a trend toward an increase in interleukin-5 (IL-5) mRNA gene transcripts in the bronchial tissue.

Nightingale et al. (2000) have reported inflammatory changes in healthy volunteers exposed to 200 $\mu g/m^3$ resuspended DPM under resting conditions in a double-blinded study. Small but statistically significant increases in neutrophils and myeloperoxidase (an index of neutrophil activation) were observed in sputum samples induced 4 hours after exposure to DPM in comparison to air. Exhaled carbon monoxide was measured as an index of oxidative stress and was found to increase maximally at 1 hour after exposure. These biochemical and cellular changes occurred in the absence of any decrements in pulmonary function, thus confirming that markers of inflammation are more sensitive than pulmonary function measurements.

Because of the considerable concern about inhalation of ambient particles by sensitive subpopulations, Sandstrom's laboratory also studied the effect of a 1 hour exposure to 300 $\mu g/m^3$ DPM on 14 atopic asthmatics with stable disease and on inhaled corticosteroid treatment (Nordenhäll et al., 2001). At 6 hours after exposure, there was a significant increase in IL-6 in induced sputum. At 24 hours after exposure, there was a significant increase in the nonspecific airway responsiveness to inhaled methacholine. Although the exposure level was high relative to ambient PM levels, these findings may be important in terms of supporting epidemiologic evidence for increased asthma morbidity associated with episodic exposure to ambient PM.

The role of antioxidant defenses in protecting against acute diesel exhaust exposure has also been studied. Blomberg et al. (1998) investigated changes in the antioxidant defense network within the respiratory tract lining fluids of human subjects following diesel exhaust exposure. Fifteen healthy, nonsmoking, asymptomatic subjects were exposed to filtered air or diesel exhaust (DPM 300 mg/m^3) for 1 h on two separate occasions at least 3 weeks apart. Nasal lavage fluid and blood samples were collected prior to, immediately after, and 5.5 h post-exposure. Bronchoscopy was performed 6 h after the end of diesel exhaust exposure. Nasal lavage ascorbic acid concentration increased tenfold during diesel exhaust exposure, but returned to basal levels 5.5 h post-exposure. Diesel exhaust had no significant effects on nasal lavage uric acid or GSH concentrations and did not affect plasma, bronchial wash, or bronchoalveolar lavage antioxidant concentrations or malondialdehyde or protein carbonyl concentrations. The authors concluded that the acute increase in ascorbic acid in the nasal cavity induced by diesel exhaust may help prevent further oxidant stress in the upper respiratory tract of healthy individuals.

7.2.1.3 Complex Combustion-Related Particles

Because emission sources contribute to the overall ambient air particulate burden (Spengler and Thurston, 1983), many of the studies investigating the response of laboratory animals to particle exposures have used complex combustion-related particles (see Table 7-2).
For example, the residual oil fly ash (ROFA) samples used in toxicological studies have been collected from a variety of sources, e.g., boilers, bag houses used to control emissions from power plants, and from particles emitted downstream of such collection devices. ROFA has a high content of water soluble sulfate and metals, accounting for 82 to 92% of water-soluble

mass, while the water-soluble mass fraction in ambient air varies from low teens to more than 60% (Costa and Dreher, 1997; Prahalad et al., 1999). More than 90% of the metals in ROFA are transition metals; whereas these metals are only a small subfraction of the total ambient PM mass. Transition metals generate reactive oxygen species and are relevant to understanding the mechanisms of toxicity and the components contributing to the toxic responses. Thus, the dose of bioavailable metal that is delivered to the lung when ROFA is instilled into a laboratory animal can be orders of magnitude greater than an ambient PM dose, even under a worst-case scenario.

Intratracheal instillation of various doses of ROFA suspension has been shown to produce severe inflammation, an indicator of pulmonary injury that includes recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA in rats have been shown to depend on aqueous leachable chemical constituents of the particles (Dreher et al., 1997; Kodavanti et al., 1997b). A leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension (Dreher et al., 1997). Depletion of Fe, Ni, and V from the ROFA leachate eliminated its pulmonary toxicity. Correspondingly, minimal lung injury was observed in animals exposed to saline-washed ROFA particles. A surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA. Interestingly, ferric sulfate and vanadium sulfate antagonized the pulmonary toxicity of nickel sulfate. Interactions between different metals and the acidity of PM were found to influence the severity and kinetics of lung injury induced by ROFA and its soluble transition metals.

To further investigate the response to ROFA with differing metal and sulfate composition, male Sprague-Dawley rats (60 days old) were intratracheally instilled with ROFA (2.5 mg/rat) or metal sulfates (iron – 0.54 μmole/rat, vanadium – 1.7 μmole/rat, and nickel – 1.0 μmole/rat, individually or in combination) (Kodavanti et al., 1997b). Transition metal sulfate mixtures caused less injury than ROFA or Ni alone, suggesting metal interactions. This study also showed that V-induced effects were less severe than that of Ni and were transient. Ferric sulfate was least pathogenic. Cytokine gene expression was induced prior to the pathology changes in the lung, and the kinetics of gene expression suggested persistent injury by nickel sulfate. Another study by the same investigators was performed using 10 different ROFA samples collected at various sites within a power plant burning residual oil (Kodavanti et al., 1998a).

Animals received intratracheal instillations of either saline (control), or a saline suspension of whole ROFA (< 3.0 μm MMAD for all ground PM) at three doses (0.833, 3.33, or 8.33 mg/kg). This study showed that ROFA-induced PMN influx was associated with its water-leachable V content; but protein leakage was associated with water-leachable Ni content. ROFA-induced in vitro activation of alveolar macrophages (AMs) was highest with ROFA containing leachable V but not with Ni plus V, suggesting that the potency and the mechanism of pulmonary injury may differ between emissions containing bioavailable V and Ni.

Other studies have shown that soluble metal components play an important role in the toxicity of emission source particles. Gavett et al. (1997) investigated the effects of two ROFA samples of equivalent diameters, but having different metal and sulfate content, on pulmonary responses in Sprague-Dawley rats. ROFA sample 1 (R1) (the same emission particles used by Dreher et al. [1997]) had approximately twice as much saline-leachable sulfate, nickel, and vanadium, and 40 times as much iron as ROFA sample 2 (R2); whereas R2 had a 31-fold higher zinc content. Rats were instilled with suspensions of 2.5 mg R2 in 0.3 mL saline, the supernatant of R2 (R2s), the supernatant of 2.5 mg R1 (R1s), or saline only. By 4 days after instillation, 4 of 24 rats treated with R2s or R2 had died. None treated with R1s or saline died. Pathological indices, such as alveolitis, early fibrotic changes, and perivascular edema, were greater in both R2 groups. In surviving rats, baseline pulmonary function parameters and airway hyperreactivity to acetylcholine were significantly worse in the R2 and R2s groups than in the R1s groups. Other than BAL neutrophils, which were significantly higher in the R2 and R2s groups, no other inflammatory cells (macrophages, eosinophils, or lymphocytes) or biochemical parameters of lung injury were significantly different between the R2 and R2s groups and the R1s group. Although (a) soluble forms of zinc had been found in guinea pigs to produce a greater pulmonary response than other sulfated metals (Amdur et al., 1978) and (b) the level of zinc was 30-fold greater in R2 than R1, the precise mechanisms by which zinc may induce such responses are unknown. Still, these results show that the composition of soluble metals and sulfate is critical in the development of airway hyperractivity and lung injury produced by ROFA, albeit at very high instilled doses.

Dye et al. (1997) pretreated rats with an intraperitoneal injection of 500 mg/kg dimethylthiourea (DMTU) or saline, followed 30 min later by intratracheal instillation of either acidic saline (Ph = 3.3) or an acidified suspension of ROFA (500 μg/rat). Dimethylthiourea

reduces the activity of the reactive oxygen species. The systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA but did not ameliorate biochemical alterations in BAL fluid. In a subsequent study, it was determined that oxidant generation, possibly induced by soluble vanadium compounds in ROFA, is responsible for the subsequent rat tracheal epithelial cells gene expression, inflammatory cytokine production (MIP-2 and IL-6), and cytotoxicity (Dye et al., 1999).

In addition to transition metals, other components in fly ash also may cause lung injury. The effects of arsenic compounds in coal fly ash or copper smelter dust on the lung integrity and on the ex vivo release of TNFα by alveolar phagocytes were investigated by Broeckaert et al. (1997). Female Naval Medical Research Institute (NMRI) mice were instilled with different particles normalized for the arsenic content (20 μg/kg body weight [i.e., 600 ng arsenic/mouse]) and the particle load (100 mg/kg body weight [i.e., 3 mg/mouse]). Mice received tungsten carbide (WC) alone, coal fly ash (CFA) alone, copper smelter dust (CMP) mixed with WC, and $Ca_3(AsO_4)_2$ mixed with WC (see Table 7-2 for concentration details). Copper smelter dust caused a severe but transient inflammatory reaction; whereas a persisting alveolitis (30 days postexposure) was observed after treatment with coal fly ash. In addition, TNFα production in response to lipopolysaccharide (LPS) by alveolar phagocytes were significantly inhibited at day 1 but was still observed at 30 days after administration of CMP and CFA. Although arsenic was cleared from the lung tissue 6 days after $Ca_3(AsO_4)_2$ administration, a significant fraction persisted (10 to 15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at Day 30. It is possible that suppression of TNF-α production is dependent upon the slow elimination of the particles and their metal content from the lung.

In summary, intratracheally instilled high doses of ROFA produced acute lung injury and inflammation. Water soluble metals in ROFA appear to play a key role in the acute effects of instilled ROFA through the production of reactive oxygen species. Although studies done with ROFA clearly show that combustion-generated particles with a high metal content can cause substantial lung injury, there are still insufficient data to extrapolate the high dose effects to the low levels of particle-associated transition metals in ambient PM.

7.2.2 Acid Aerosols

There have been extensive studies of the effects of controlled exposures to aqueous acid aerosols on various aspects of lung function in humans and laboratory animals. Many of these studies were reviewed in the 1996 PM AQCD (U.S. Environmental Protection Agency 1996a) and in the Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989); some of the more recent studies are summarized in this document (Table 7-4). Methodology and measurement methods for controlled human exposure studies have been reviewed elsewhere (Folinsbee et al., 1997).

The studies summarized in the 1996 PM AQCD illustrate that aqueous acidic aerosols have minimal effects on symptoms and mechanical lung function in young healthy adult volunteers at concentrations as high as 1000 $\mu g/m^3$. However, at concentrations as low as 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. Brief exposures ($\leq$ 1 h) to low concentrations ($\approx$ 100 $\mu g/m^3$) may accelerate clearance while longer (multihour) exposures to higher concentrations (> 100 $\mu g/m^3$) can depress clearance. Asthmatic subjects appear to be more sensitive to the effects of acidic aerosols on mechanical lung function. Responses have been reported in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$, and modest bronchoconstriction has been seen in adult asthmatics exposed to concentrations $\geq$400 $\mu g/m^3$, but the available data are not consistent.

Acid aerosol exposure in humans (1000 $\mu g/m^3$ H_2SO_4) did not result in airway inflammation (Frampton et al., 1992), and there was no evidence of altered macrophage host defenses. Zelikoff et al. (1997) compared the responses of rabbits and humans exposed to similar concentrations of H_2SO_4 aerosol. For both rabbits and humans, there was no evidence of PMN infiltration into the lung and no change in BAL fluid protein level, although there was an increase in LDH in rabbits but not in humans. Macrophages showed less antimicrobial activity in rabbits; insufficient data were available for humans. Macrophage phagocytic activity was slightly reduced in rabbits but not in humans. Superoxide production by macrophages was somewhat depressed in both species. No respiratory effects of long-term exposure to acid aerosol were found in dogs (Heyder et al., 1999). Thus, recent studies do not provide any additional evidence clearly demonstrating that relevant concentrations of aqueous acid aerosols contribute to the acute cardiopulmonary effects of ambient PM.

TABLE 7-4. 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/m^3	1.0 µm MMAD σg = 2.2	16.5 h/day for 13 mo	Long-term exposure to particle-associated sulfur and hydrogen ions caused only subtle respiratory responses and no change in lung pathology.	Heyder et al. (1999)
	Acidic sulfate aerosol	Inhalation	5.7 mg/m^3	1.1 µm MMAD σg = 2.0	6 h/day for 13 mo		
Humans, asthmatic; 13 M, 11 F	H_2SO_4 aerosol NH^+_4/SO^{-2}_4 aerosol	Inhalation by face mask	500 µg/m^3	9 µm MMAD 7 µm MMAD	1 h	Exposure to simulated natural acid fog did not induce bronchoconstriction nor change bronchial responsiveness in asthmatics.	Leduc et al. (1995)
Rats, female, Fischer 344; Guinea Pigs, female, Hartley	H_2SO_4 aerosol	Inhalation	94 mg/m^3 43 mg/m^3	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/m^3	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%.	Frampton et al. (1992)
Rabbits, New Zealand white	H_2SO_4	Inhalation	1,000 µg/m^3		2 h	No inflammatory response; antibody mediated cytotoxicity of AM increased by H_2SO_4; no alterations in antimicrobial defense.	Zelikoff et al. (1997)
Humans, healthy nonsmokers; 12 m, 20-39 years old							

H_2SO_4 = Sulfuric acid
BAL = Bronchoalveolar lavage
LDH = Lactate dehydrogenase
MMAD = Mass median aerodynamic diameter
MMD = Mass median diameter
σg = Geometric standard deviation

DRAFT-DO NOT QUOTE OR CITE

7.2.3 Metal Particles, Fumes, and Smoke

Data from occupational and laboratory animal studies reviewed in the previous criteria document (U. S. Environmental Protection Agency, 1996a) indicated that acute exposures to very high levels (hundreds of $\mu g/m^3$ or more) or chronic exposures to lower levels (as low as 15 $\mu g/m^3$) of metallic particles could have an effect on the respiratory tract. Therefore, it was concluded on the basis of data available at that time that the metals at typical concentrations present in the ambient atmosphere (1 to 14 $\mu g/m^3$) were not likely to have a significant acute effect in healthy individuals. The metals include arsenic, cadmium, copper, nickel, vanadium, iron, and zinc. Other metals found at concentrations less than 0.5 $\mu g/m^3$ were not reviewed in the previous criteria document. However, more recently published data from high-dose laboratory animal studies tend to indicate that particle-associated metals are among likely potential candidates for inducing adverse effects attributed to ambient PM.

Controlled human exposure studies have been performed with particles other than acid aerosols (details are in Table 7-5a,b). Controlled inhalation exposure studies to high concentrations of two different fume particles, MgO and ZnO, demonstrate the differences in response based on particle metal composition (Kuschner et al., 1997; Kuschner et al., 1995). Up to 6400 mg/m^3/min cumulative dose of MgO had no effect on lung function (spirometry, $D_{L_{CO}}$), symptoms of metal fume fever, or changes in inflammatory mediators or cells recovered by BAL. However, lower concentrations of ZnO fume (166 to 1110 mg/m^3/min) induced a neutrophilic inflammatory response in the airways 20 h postexposure. Lavage fluid PMNs, TNF-α, and IL-8 were increased by ZnO exposure. Although the concentrations used in these exposure studies exceed ambient levels by more than 1000-fold, the absence of a response to an almost 10-fold higher concentration of MgO compared with ZnO indicates that differential metal composition, in addition to particle size (ultrafine/fine), is likely an important determinant of observed health responses to inhaled ambient PM.

Several metals (e.g., zinc, chromium, cobalt, copper, and vanadium) have been shown to stimulate cytokine release in cultured human pulmonary cells. Boiler makers, exposed occupationally to ~400 to 500 $\mu g/m^3$ of fuel oil ash, containing high levels of soluble metals, showed acute nasal inflammatory responses characterized by increased myeloperoxidase (MPO) and IL-8 levels; these changes were associated with increased vanadium levels in the upper

TABLE 7-5a. RESPIRATORY EFFECTS OF INSTILLED METAL PARTICLES, FUMES, AND SMOKE IN HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Humans, healthy nonsmokers; 12 M, 4 F; 18-35 years old	Colloidal iron oxide	Bronchial instillation	5 mg in 10 mL	2.6 µm	1, 2, and 4 days after instillation	L-ferritin increased after iron oxide particle exposure; transferrin was decreased. Both lactoferrin and transferrin receptors were increased.	Ghio et al. (1998b)
Humans, healthy nonsmokers; 27 M, 7 F; 20-36 years old	Fe_2O_3	Intrapulmonary instillation	3×10^8 microspheres in 10 mL saline.	2.6 µm	N/A	Transient inflammation induced initially (neutrophils, protein, LDH, IL-8) was resolved by 4 days postinstillation.	Lay et al. (1998)
Mice, Swiss	EHC-93 soluble metal salts	Intratracheal instillation	1 mg in 0.1 ml	0.8 ± 0.4 µm	3 days	Solution containing all metal salts (Al, Cu, Fe, Pb, Mg, Ni, Zn) or ZnCl alone increased BAL inflammatory cells and protein.	Adamson et al. (2000)
Rats, Fischer 344. (250 g)	Fe_2O_3	Intratracheal instillation	7.7×10^7 microspheres in 5 mL saline	2.6 µm	N/A	Transient inflammation at 1 day postinstillation.	Lay et al. (1998)
Mice, NMRI; Mouse peritoneal macrophage	MnO_2	Intratracheal instillation; in vitro	0.037, 0.12, 0.75, 2.5 mg/animal	surface area of 0.16, 0.5; 17, 62 m^2/g	Sacrificed at 5 days	LDH, protein and cellular recruitment increased with increasing surface area; freshly ground particles had enhanced cytotoxicity.	Lison et al. (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	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_2O_5	Intratracheal instillation	21 or 210 µg V/kg ($NaVO_3$, $VOSO_4$ soluble) 42 or 420 µg V/kg (V_2O_s) less soluble	N/A	1 h or 10 days following instillation	PMN influx was greatest following $VOSO_4$, lowest for V_2O_5; $VOSO_4$ 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)

CdO = Cadmium oxide
Fe_2O_3 = Iron oxide
MgO = Magnesium oxide
MnO_2 = Manganese oxide
$NaVO_3$ =
TiO_2 = Titanium oxide
$VOSO_4$ = Vanadyl sulfate
V_2O_5 = Vanadium oxid
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

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-5b. RESPIRATORY EFFECTS OF INHALED 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, SD; 60 days old	VSO_4 $NiSO_4$	Inhalation	0.3 - 2.4 mg/m^3	N/A	6h/day x 4 days	V did not induce any significant changes in BAL or HR; Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at > 1.2 mg/m^3; possible synergistic effects were found.	Campen et al. (2001)
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)
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)
Humans, vanadium plant workers; 40 M; 19-60 years old	V_2O_5	Inhalation	< 0.05-1.53 mg/m^3	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	Inhalation	5.8-230 mg/m^3	99% < 1.8 µm 29% < 0.1 µm	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; 8 M, 8 F; 18-34 years old	Fe_2O_3	Inhalation	12.7 mg/m^3	1.5 µm σg = 2.1	30 min	No significant difference in $^{98m}T_c$-DTPA clearance half-times, D_LCO, or spirometry	Lay et al. (2001)

CdO = Cadmium oxide
Fe_2O_3 = Iron oxide
MgO = Magnesium oxide
MnO_2 = Manganese oxide
$NaVO_3$ =
TiO_2 = Titanium oxide
$VOSO_4$ = Vanadyl sulfate
V_2O_5 = Vanadium oxid
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

DRAFT-DO NOT QUOTE OR CITE

airway (Woodin et al., 1998). Also, Irsigler et al. (1999) reported that V_2O_5 can induce asthma and bronchial hyperreactivity in exposed workers.

Autopsy data suggest that chronic exposure to urban air pollution leads to an increased retention of metals in human tissues. A comparison of autopsy cases in Mexico City from the 1950s with the 1980s indicated substantially higher (5- to 20-fold) levels of Cd, Co, Cu, Ni, and Pb in lung tissue from the 1980s (Fortoul et al., 1996). Similar studies have examined metal content in human blood and lung tissue (Tsuchiyama et al., 1997; Osman et al., 1998), with similar results.

Iron is the most abundant of the elements capable of catalyzing oxidant generation and is also present in ambient urban particles. Lay et al. (1998) and Ghio et al. (1998b) tested the hypothesis that the human respiratory tract will attempt to diminish the added, iron-generated oxidative stress. They examined cellular and biochemical responses of human subjects instilled, via the intrapulmonary route, with a combination of iron oxyhydroxides that introduced an oxidative stress to the lungs. Saline alone and iron-containing particles suspended in saline were instilled into separate lung segments of human subjects. Subjects underwent bronchoalveolar lavage at 1 to 91 days after instillation of 2.6-μm diameter iron oxide (approximately 5 mg or 2.1×10^8 particles) agglomerates. Lay and colleagues found iron-oxide-induced inflammatory responses in both the alveolar fraction and the bronchial fraction of the lavage fluid at 1 day postinstillation. Lung lavage 24 h after instillation revealed decreased transferrin concentrations and increased ferritin and lactoferrin concentrations, consistent with a host-generated response to decrease the availability of catalytically reactive iron (Ghio et al., 1998b). Normal iron homeostasis returned within 4 days of the iron particle instillation. The same iron oxide preparation, which contained a small amount of soluble iron, produced similar pulmonary inflammation in rats. In contrast, instillation of rats with two iron oxide preparations that contained no soluble iron failed to produce injury or inflammation, thus suggesting that soluble iron was responsible for the observed intrapulmonary changes.

In a subsequent inhalation study, Lay et al. (2001) studied the effect of iron oxide particles on lung epithelial cell permeability. Healthy, nonsmoking human subjects inhaled 12.7 mg/m^3 low- and high-solubility iron oxide particles (MMAD = 1.5 μm and σg = 2.1) for 30 minutes. Neither pulmonary function nor alveolar epithelial permeability, as assessed by pulmonary clearance of technetium-labeled DPTA, was changed at 0.5 or 24 hours after exposure to either

type of iron oxide particle. Because the exposure concentration was so high, the data suggest that iron may play little role in the adverse effects of ambient, urban PM. Ghio et al. (2001) have reported a case study, however, in which acute exposure to oil fly ash from a domestic oil-burning stove produced diffuse alveolar damage, difficulty in breathing, and symptoms of angina. While steroid treatment led to rapid improvement in symptoms and objective measurements, this report suggests that the high metal content of oil fly ash can alter the epithelial cell barrier in the alveolar region.

7.2.4 Ambient Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxins, and plant and animal debris. Such biological aerosols can produce various health effects including irritation, infection, hypersensitivity, and toxic response. Bioaerosols present in the ambient environment have the potential to cause disease in humans under certain conditions. However, it was concluded in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) that bioaerosols, at the concentrations present in the ambient environment, would not likely contribute to the observed effects of PM on human mortality and morbidity reported in PM epidemiologic studies. Moreover, bioaerosols generally represent a rather small fraction of the measured urban ambient PM mass and are typically present even at lower concentrations during the winter months when notable ambient PM effects have been demonstrated. Bioaerosols tend to be in the coarse fraction of PM, but some bioaerosols, including nonagglomerated bacteria and fragmented pollens, are found in the fine fraction.

More recent inhalation studies on ambient bioaerosols are summarized in Table 7-6. The majority of these studies have focused on endotoxin, because little research on other bioaerosol components has been conducted. In vitro studies on particle-associated endotoxin are discussed in Section 7.5.2.2. Endotoxin, a cell wall component of gram negative bacteria, is ubiquitous in the environment. Although there is strong evidence that inhaled endotoxin plays a major role in the toxic effects of bioaerosols encountered in the work place (Vogelzang et al., 1998; Castellan et al., 1984, 1987), it is not clear whether ambient concentrations of endotoxin are sufficient to produce toxic pulmonary or systemic effects in healthy or compromised individuals.

Michel et al. (1997) examined the dose-response relationship to inhaled lipopolysaccharide (LPS: the purified derivative of endotoxin) in normal healthy volunteers exposed to 0, 0.5, 5, and

TABLE 7-6. CONTROLLED EXPOSURE STUDIES OF RESPIRATORY EFFECTS OF INHALED 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 22 months old, N = 3/group	LPS (endotoxin)	Inhalation	70 EU	0.72 µm σg = 1.6	12 min	Significant increase in PMNs in bronchoalveolar lavage (BAL) in LPS exposed animals. LPS significantly affected the reactive oxygen species activity in BAL. Effects were age-dependent.	Elder et al. (2000a,b)
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 Endotoxin	Inhalation	2.63 mg/m^3 σg = 1.3 105 ng/m^3 σg = 1.5	N/A	5 h/day average lifetime exposure	Large decline in FEV_1 (73 mL/year) and FVC (55 mL/year) associated with long-term average exposure to endotoxin.	Vogelzang et al. (1998)
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 (≈ 4.5 ng/m^3) over 8 h.	Zock et al. (1998)

DRAFT-DO NOT QUOTE OR CITE

50 μg of LPS. Inhalation of 5 or 50 μg of LPS resulted in increased PMNs in blood and sputum samples. At the higher concentration, a slight (3%) but not significant decrease in FEV_1 was observed. Cormier et al. (1998) reported an approximate 10% decline in FEV_1 and an increase in methacholine airway responsiveness after a 5-h exposure inside a swine containment building. This exposure induced significant neutrophilic inflammation in both the nose and the lung. Although these exposures are massive compared to endotoxin levels in ambient PM in U.S. cities, these studies serve to illustrate the effects of endotoxin and associated bioaerosol material in healthy, nonsensitized individuals.

Some health effects have been observed after occupational exposure to complex aerosols containing endotoxin at concentrations relevant to ambient levels. Zock et al. (1998) reported a decline in FEV_1 (≈ 3%) across a shift in a potato processing plant with up to 56 endotoxin units (EU)/m^3 in the air. Rose et al. (1998) reported a high incidence (65%) of BAL lymphocytes in lifeguards working at a swimming pool where endotoxin levels in the air were on the order of 28 EU/m^3. Although these latter two studies may point towards pulmonary changes at low concentrations of airborne endotoxin, it is not possible to rule out the contribution of other agents in these complex organic aerosols. The contribution of endotoxin to the toxicity of ambient PM has been studied in vitro, and these studies provide some evidence that endotoxin contaminates in ambient PM may play a role in the observed in vitro effects (discussed in Section 7.5).

7.3 CARDIOVASCULAR AND SYSTEMIC EFFECTS OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES

A growing number of epidemiology studies have demonstrated that increases in cardiac-related deaths are associated with exposure to PM (U.S. Environmental Protection Agency, 1996a) and that PM-related cardiac deaths appear to be as great or greater than those attributed to respiratory causes (see Chapter 8). The toxicological consequences of inhaled particles on the cardiovascular system had not been extensively investigated prior to 1996. Since then (see Table 7-7a,b), Costa and colleagues (e.g., Costa and Dreher, 1997) have demonstrated that intratracheal instillation of high levels of ambient particles can increase or accelerate death in an animal model of cardiorespiratory disease that followed monocrotaline administration in rats.

TABLE 7-7a. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
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)
Rats, male, S-D, 60 days old, MCT-treated, and healthy	Emission source PM	Instillation	Total mass: 2.5 mg/rat	Emission PM: 1.78-4.17 µm	Analysis at 24 and 96 h following instillation	ROFA alone induced some mild arrhythumas; MCT-ROFA showed enhanced neutrophilic inflammation.	Costa and Dreher (1997)
	Ambient airshed PM ROFA		Total transition metal: 46 µg/rat	Ambient PM: 3.27-4.09 µm		MCT-ROFA animals showed more numerous and severe arrhythmias including S-T segment inversions and A-V block.	
Rats, male, S-D; 60 days old	ROFA	Instillation	0.3, 1.7, or 8.3 mg/kg	1.95 µm $\sigma g = 2.19$	Analysis at 24 h	Increased plasma fibrinogen at 8.3 mg/kg only.	Gardner et al. (2000)
Rats, male SH and WKY; 12-13 weeks old	ROFA from a precipitator of an oil-burning power plant	Intratracheal instillation	1 and 5 mg/kg	1.5 µm $\sigma_g = 1.5$	Analysis at 1, 2, and 4 days	Exposure increased plasma fibrinogen and decreased peripheral lymphocytes in both SH and WKY rats.	Kodavanti et al. (2002)
Rabbits, female, New Zealand White, 1.8 to 2.4 kg	Colloidal carbon	Instillation	2 mL of 1% colloidal carbon (20 mg)	< 1 µm	Examined 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, male, S-D, MCT-treated	ROFA	Instillation	0.25, 1.0, or 2.5 mg in 0.3 mL saline	1.95 µm MMAD $\sigma g = 2.19$	Monitored for 96 h after instillation of ROFA particles	Dose-related increases in 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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-7a (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	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 $\sigma g = 2.19$	Monitored for 96 h after instillation	(1) Healthy rats exposed IT to ROFA demonstrated dose-related hypothermia, bradycardia, and increased arrhythmias. 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.	Watkinson et al. (2000a,b); Watkinson et al (2001)
(2) Rats, SH, 15-mo-old	OTT ROFA MSH	Intratracheal instillation	2.5 mg 0.5 mg 2.5 mg			(2) Older rats exposed IT to OTT showed a pronounced biphasic hypothermia and a severe drop in HR accompanied by increased arrhythmias; exposure to ROFA caused less pronounced, but similar effects. No cardiac effects were seen with exposure to MSH.	
(3) Rats, S-D MCT-treated	$Fe_2(SO_4)_3$ VSO_4 $NiSO_2$	Intratracheal instillation	105 μg 245 μg 262.5 μg			(3) Ni and V showed the greatest toxicity; Fe-exposed rats did not differ from controls.	

[a]ROFA = Residual oil fly ash
OTT = Ottawa dust
$Fe_2(SO_4)_3$ = Iron sulfate
MSH = Mt. St. Helen's volcanic ash
VSO_4 = Vanadium sulfate
$NiSO_2$ = Nickel sulfate

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-7b. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INHALED AMBIENT AND COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
Dogs, beagles, 10.5-year- old, healthy, n = 4	ROFA	Oral inhalation	3 mg/m^3	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. (2000a)
Rats, male, F-344; 200-250 g	OTT	Nose-only Inhalation	40 mg/m^3	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)
Dogs, female mongrel, 14 to 17 kg	CAPs	Inhalation via tracheostomy	3-360 µg/m^3	0.2 to 0.3 µm	6 h/day for 3 days	Peripheral blood parameters were related to specific particle constituents. Factor analysis from paired and crossover experiments showed that hematologic changes were not associated with increases in total CAP mass concentration.	Clarke et al. (2000a)
Humans, healthy nonsmokers, 18 to 40 years old	CAPs	Inhalation	23.1 to 311.1 µg/m^3	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/m^3	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/m^3	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/m^3	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/m^3	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.	Killingswort h et al. (1997)

DRAFT-DO NOT QUOTE OR CITE

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

Species, Gender, Strain Age, or Body Weight	Particle[a]	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/m^3	N/A	6 h/day for 3 days	Cardiomyopathy and monocytic cell infiltration, along with increased cytokine expression, was found in left ventricle of SH rats because of underlying cardiovascular disease. ECG showed exacerbated ST segment depression caused by ROFA.	Kodavanti et al. (2000b)
Rats, Wistar	Ottawa ambient (EHC-93) (ECH-93L) Diesel soot (DPM) Carbon black (CB)	Inhalation (nose only)	48 mg/m^3 49 mg/m^3 5 mg/m^3 5 mg/m^3	36, 56, 80, 100, and 300 µm	4 h	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, S-D, SH rats, WKY rats, healthy and MCT-treated	ROFA	Inhalation	15 mg/m^3	1.95 µm MMAD	6 h/day for 3 days	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.	Watkinson et al. (2000a,b)
Rats, male, SH and WKY; 12 to 13 weeks old	ROFA from a precipitator of an oil burning power plant	Inhalation	15 mg/m^3	1.5 µm σg = 1.5	6 h/d, 3 d/wk for 1, 2, or 4 wk	One week exposure increased plasma fibrogen in SH rats only; longer exposure caused pulmonary injury but no changes in figrogen.	Kodavanti et al. (2002)
Rats, male, S-D, healthy and MI	Boston ROFA Carbon black	Inhalation	3 mg/m^3	1.81 µm 0.95 µm	1 h	ROFA increased arrhythmia frequency in animals with preexisting premature ventricular complexes and decreased heart rate variability. Other exposed groups not affected.	Wellenius et al. (2002)

[a]ROFA = Residual oil fly ash
OTT = Ottawa dust
MSH = Mt. St. Helen's volcanic ash
$Fe_2(SO_4)_3$ = Iron sulfate
VSO_4 = Vanadium sulfate
$NiSO_2$ = Nickel sulfate
MI - Myocardial infraction

DRAFT-DO NOT QUOTE OR CITE

These deaths did not occur with all types of ambient particles tested. Some dusts, such as volcanic ash from Mount Saint Helens, were relatively inert; whereas other ambient dusts, including those from urban sites, were toxic. These early observations suggested that particle composition plays an important role in the adverse health effects associated with episodic exposure to ambient PM, despite the "general particle" effect attributed to the epidemiologic associations of ambient PM exposure and increased mortality in many regions of the United States (i.e., regions with varying particle composition). Work that examines the role of inherent susceptibility to the adverse effects of PM in compromised animal models of human pathophysiology provides a potentially important link to epidemiologic observations and is discussed below.

To date, studies examining the systemic and cardiovascular effects of particles have used a number of compromised animal models, largely rodent models. Two studies in normal or compromised dogs (Godleski et al., 2000; Muggenburg et al., 2000a) also have been published as well as the preliminary results from studies in which human subjects were exposed to concentrated ambient PM (see Section 7.4.1). Muggenburg et al. (2000b) described several potential animal models of cardiac disease (monocrotaline-induced pulmonary hypertension, dilated cardiomyopathy, viral and mycoplasmal myocarditis, and ischemic heart disease), including a discussion of the advantages and disadvantages in the use of animal models in the study of cardiac disease and air pollution. Pulmonary hypertension in humans may result from airway and vascular effects from COPD, asthma, and cystic fibrosis. The monocrotaline (MCT)-induced vascular disease model exhibits common features of chronic obstructive pulmonary disease in humans. The mechanism of injury includes selective pulmonary endothelial damage and progressive pulmonary arterial muscularization. Pulmonary hypertension develops as the blood flow is impeded. Right ventricular hypertrophy follows the pulmonary hypertension. To produce pulmonary hypertension, animals are injected subcutaneously with 50-60 mg/kg monocrotaline. Within two weeks following treatment, experimental animals, primarily rats, develop pulmonary hypertension (Kodavanti et al., 1998a). The majority of animal studies examining the systemic effects of PM have used metal-laden ROFA as a source particle, a growing number of studies have used collected and stored ambient PM or real-time generated concentrated ambient particles. The following discussion of the systemic effects of PM first

describes the studies using ROFA and then compares these findings with the ambient PM studies.

Killingsworth et al. (1997) used fuel oil fly ash to examine the adverse effects of a model urban particle using the MCT model of cardiorespiratory disease. They observed 42% mortality in MCT rats exposed to ~580 μg/m^3 fly ash for 6 h/day for 3 consecutive days. Deaths did not occur in MCT rats exposed to filtered air or in saline-treated rats exposed to fly ash. The increase in MCT/fly ash group deaths was accompanied by increased neutrophils in lavage fluid and increased immunostaining of MIP-2 in the heart and lungs of the MCT/fly ash animals. Cardiac immunohistochemical analysis indicated increased MIP-2 in cardiac macrophages. The fly ash-induced deaths did not result from a change in pulmonary arterial pressure and the cause of death was not identified.

In a similar experimental model, Watkinson et al. (1998) examined the effects of intratracheally instilled ROFA (0.0, 0.25, 1.0, 2.5 mg in 0.3 mL saline) on ECG measurements in control and MCT rats. They observed a dose-related increase in the incidence and duration of arrhythmic events in control animals exposed to ROFA particles, and these effects were clearly exacerbated in the MCT animals. Similar to the results of Killingsworth et al. (1997), healthy animals treated with ROFA suffered no deaths, but there were 1, 3, and 2 deaths in the low-, medium-, and high-dose MCT groups, respectively. Thus, ROFA PM was linked to the conductive and hypoxemic arrhythmias associated with cardiac-related deaths in the MCT animals.

To examine the biological relevance of intratracheal instillation of ROFA particles, Kodavanti et al. (1999) exposed MCT rats to ROFA by either instillation (0.83 or 3.33 mg/kg) or nose-only inhalation (15 mg/m^3, 6 h/day for 3 consecutive days). Similar to Watkinson et al. (1998), intratracheal instillation of ROFA in MCT rats resulted in ≈50% mortality. Notably, no mortality occurred in MCT rats exposed to ROFA by the inhalation route despite the high exposure concentration (15 mg/m^3). In addition, no mortality occurred in healthy rats exposed to ROFA or in MCT rats exposed to clean air. Despite the fact that mortality was not associated with ROFA inhalation exposure of MCT rats, exacerbation of lung lesions and pulmonary inflammatory cytokine gene expression, as well as ECG abnormalities, clearly were evident.

Watkinson and colleagues further examined the effect of instilled ROFA in rodents previously exposed to ozone or housed in the cold (Watkinson et al., 2000a,b; Watkinson et al.,

2001; Campen et al., 2000). The effect of ozone-induced pulmonary inflammation (preexposure to 1 ppm ozone for 6 h) or housing in the cold (10 °C) on the response to instilled ROFA in rats was similar to that produced with MCT. Bradycardia, arrhythmias, and hypothermic changes were consistently observed in the ozone exposed and hypothermic animals treated with ROFA, although, unlike in the MCT animals, no deaths occurred. Thus, in rodents with cardiopulmonary disease/stress, instillation of 0.25 mg or more of ROFA can produce systemic changes that may be used to study potential mechanisms of toxicity that are consistent with the epidemiology and panel studies showing cardiopulmonary effects in humans.

While studies of instilled residual oil fly ash demonstrated immediate and delayed responses, consisting of bradycardia, hypothermia, and arrhythmogenesis in conscious, unrestrained rats (Watkinson et al., 1998; Campen et al., 2000), further study of instilled ROFA-associated transition metals showed that vanadium induced the immediate responses, while nickel was responsible for the delayed effects (Campen et al., 2002). Moreover, Ni, when administered concomitantly, potentiated the immediate effects caused by V.

In another study, Campen et al. (2001) examined the responses to these metals in conscious rats by whole-body inhalation exposure. The authors attempted to ensure valid dosimetric comparisons with the instillation studies, by using concentrations of V and Ni ranging from 0.3-2.4 mg/m^3. The concentrations used in this study incorporated estimates of total inhalation dose derived using different ventilatory parameters. Heart rate (HR), core temperature (T[CO]), and electrocardiographic (ECG) data were measured continuously throughout the exposure. Animals were exposed to aerosolized Ni, V, or Ni + V for 6 h per day for 4 days, after which serum and bronchoalveolar lavage samples were taken. While Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at concentrations > 1.2 mg/m^3, V failed to induce any significant change in HR or T (CO), even at the highest concentration. When combined, Ni and V produced observable delayed bradycardia and hypothermia at 0.5 mg/m^3 and potentiated these responses at 1.3 mg/m^3, to a greater degree than were produced by the highest concentration of Ni (2.1 mg/m^3) alone. Although these studies were performed at metal concentrations that were orders of magnitude greater than ambient concentrations, the results indicate a possible synergistic relationship between inhaled Ni and V.

Watkinson et al. (2000a,b) also sought to examine the relative toxicity of different particles on the cardiovascular system of spontaneously hypertensive rats. They instilled 2.5 mg of

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

To more closely mimic environmental exposures, Kodavanti et al. (2000b) exposed spontaneously hypertensive (SH) and normotensive (WKY) rats to 15 mg/m^3 ROFA for 6 h/day for 3 days. The exposure concentration, while 100 times or more higher than usual current U.S. ambient air PM concentrations, was selected to produce a frank but non-lethal injury and to allow comparison to the intratracheal approaches. Exposure to ROFA produced alterations in the ECG waveform of spontaneously hypertensive (SH) but not normotensive rats. Although the ST segment area of the ECG was depressed in the SH rats exposed to air, further depressions in the ST segment were observed at the end of the 6-h exposure to ROFA on Days 1 and 2. The enhanced ST segment depression was not observed on the third day of exposure, suggesting that adaptation to the response had occurred. Thus, exposure to a very high concentration of ROFA exacerbated a defect in the electroconductivity pattern of the heart in an animal model of hypertension. This ROFA-induced alteration in the ECG waveform was not accompanied by an enhancement in the monocytic cell infiltration and cardiomyopathy that also develop in SH rats. Further work is necessary to determine the relevance of this ROFA study to PM at concentrations relevant to ambient exposures.

Godleski and colleagues (2000a) have performed a series of experiments examining the cardiopulmonary effects of inhaled concentrated ambient PM on normal mongrel dogs and on dogs with coronary artery occlusion. Dogs were exposed by inhalation via a tracheostomy tube to concentrated ambient PM for 6 h/day for 3 consecutive days. The investigators found little biologically-relevant evidence of pulmonary inflammation or injury in normal dogs exposed to

PM (daily range of mean concentrations was ~100 to 1,000 μg/m^3). The only statistically significant effect was a doubling of the percentage of neutrophils in lung lavage. Despite the absence of major pulmonary effects, a significant increase in heart rate variability (an index of cardiac autonomic activity), a decrease in heart rate, and an increase in T alternans (an index of vulnerability to ventricular fibrillation) were seen. Exposure assessment of particle composition produced no specific components of the particles that were correlated with the day-to-day variability in response. The significance of these effects is not yet clear, because the effects did not occur on all exposure days. For example, the change in heart rate variability was observed on only 10 of the 23 exposure days. Although the heart rate variability change and the increase in T alternans suggest a possible proarrhythmic response to inhaled concentrated ambient PM, the clinical significance of this effect is currently unknown.

The most important finding of Godleski et al. (2000) was the observation of a potential increase in ischemic stress of the cardiac tissue from repeated exposure to concentrated ambient PM. During coronary occlusion in four dogs exposed to PM, they observed a significantly more rapid development of ST elevation of the ECG waveform. Also, the peak ST-segment elevation was greater after PM exposure. Together, these changes suggest that concentrated ambient PM can augment the ischemia associated with coronary artery occlusion in this dog model. More work in more dogs as well as other species is necessary to determine the significance of these findings to the human response to ambient PM.

Muggenburg and colleagues (2000a) reported that inhalation exposure to high concentrations of ROFA produces no consistent changes in amplitude of the ST-segment, form of the T wave, or arrhythmias in dogs. In their studies, four beagle dogs were exposed to 3 mg/m^3 ROFA particles for 3 h/day for 3 consecutive days. They noted a slight but variable decrease in heart rate, but the changes were not statistically or biologically significant. The transition metal content of the ROFA used by Muggenburg was ~15% by mass, a value on the order of a magnitude higher than that found in ambient urban PM samples. Although the study did not specifically address the effect of metals, it suggests that inhalation of high concentrations of metals may have little effect on the cardiovascular system of a healthy individual.

In a series of studies, (Gordon et al., 2000) examined the response of the rodent cardiovascular system to concentrated ambient PM derived from New York City air. Particles of 0.2 to 2.5 μm diameter were concentrated up to 10 times their levels in ambient air (≈150 to

900 μg/m^3) to maximize possible differences in effects between normal and cardiopulmonary-compromised laboratory animals. ECG changes were not detected in normal Fischer 344 rats or hamsters exposed by inhalation to concentrated ambient PM for 1 to 3 days. Similarly, no deaths or ECG changes were seem in MCT rats or cardiomyopathic hamsters exposed to PM. In contrast, to the nonsignificant decrease in heart rate observed in dogs exposed to concentrated ambient PM (Godleski et al., 2000), heart rate was increased significantly in both normal and MCT rats exposed to PM. The increase was approximately 5% and statistically significant, but was not observed on all exposure days. Thus, extrapolation of the heart rate changes in these animal studies to human health effects is difficult, although the increase in heart rate in rats is similar to that observed in some human population studies.

Gordon and colleagues (1998) have reported other cardiovascular effects in animals exposed to inhaled CAP. Increases in peripheral blood platelets and neutrophils were observed in control and MCT rats at 3 h, but not 24 h, after exposure to 150 to 400 μg/m^3 concentrated ambient PM (CAP). This neutrophil effect did not appear to be dose-related and did not occur on all exposure days, suggesting that day-to-day changes in particle composition may play an important role in the systemic effects of inhaled particles. The number of studies reported was small; and, it is therefore not possible to statistically determine if the day-to-day variability was truly due to differences in particle composition or even to determine the size of this effect. Terashima et al. (1997) also examined the effect of particles on circulating neutrophils. They instilled rabbits with 20 mg colloidal carbon, a relatively inert particle (< 1 μm), and observed a stimulation of the release of 5'-bromo-2'deoxyuridine (BrdU)-labeled PMNs from the bone marrow at 2 to 3 days after instillation. Because the instilled supernatant from rabbit AMs treated in vitro with colloidal carbon also stimulated the release of PMNs from the bone marrow, the authors hypothesized that cytokines released from activated macrophages could be responsible for this systemic effect. The same research group (Tan et al., 2000) looked for increased white blood cell counts as a marker for bone marrow PMN precursor release in humans exposed to very high levels of carbon from biomass burning during the 1997 Southeast Asian smoke-haze episodes. They found a significant association between PM_{10} (1-day lag) and elevated band neutrophil counts expressed as a percentage of total PMNs. The biological relevance of this latter study more usual urban PM exposure-induced systemic effects is unclear; however, because of the high dose of carbon particles.

The results of epidemiology studies suggest that homeostatic changes in the vascular system can occur after episodic exposure to ambient PM. Studies by Vincent et al. (2001) indicate that urban particles inhaled by laboratory rats can affect blood levels of endothelin and cause a vasopressor response without causing acute lung injury. Moreover, the potency to influence hemodynamic changes can be modified by removing the polar organic compounds and soluble elements from the particles. Frampton (2001) exposed healthy, nonsmoking subjects (18 to 55 years old) to 10 $\mu g/m^3$ ultrafine carbon while resting. Subjects were exposed to the ultrafine carbon through a mouthpiece for 2 h with a ten minute break between each hour exposure. The exposure concentration (10 $\mu g/m^3$) corresponded to 2×10^6 particles/cm^3. Subjects were assessed for respiratory symptoms, spirometry, blood pressure, pulse-oximetry, blood markers, and exhaled NO before, immediately following, and 3.5 and 21 h post-exposure. Blood markers focused on parameters related to acute response, blood coagulation, circulating leukocyte activation, including complete blood leukocyte counts and differentials, IL-6, fibrinogen, and clotting factor VII. Heart rate variability and repolarization phenomena were evaluated by continuous 24-h Holter monitoring. Preliminary findings indicated no particle-related symptoms. In a study described previously (Section 7.2.3), Ghio et al. (2000a) also showed that inhalation of concentrated PM in healthy nonsmokers causes increased levels of blood fibrinogen. They exposed 38 volunteers exercising intermittently at moderate levels of exertion for 2 h to either filtered air or particles concentrated from the air in Chapel Hill, NC (23 to 311 $\mu g/m^3$). Blood obtained 18 h after exposure contained significantly more fibrinogen than blood obtained before exposure. The observed effects in blood may be associated with the mild pulmonary inflammation also found 18 h after exposure to CAP (see Section 7.2.3).

Zelikoff et al. (2003) reported that CAPs had relatively little effect on the pulmonary or systemic immune defense mechanisms in Fisher rats exposed to 0 or 90 to 600 $\mu g/m^3$ for 3 h prior to IT instillation of Streptococcus pneumoniae ($2 - 4 \times 10^7$ organisms delivered dose). The number of lavageable cells, PAM and PMN, increased in both experimental groups but were twice as high in the CAPs exposed groups and were elevated faster and remained elevated longer. Lymphocyte values and WPC were significantly increased 24 and 72 h postinfection in both groups. CAPs exposure retarded the decline of TNFα and IL-6 levels three days postinfection compared to bacteria only exposed rats, however, the differences were not

significant. CAPs exposure significantly increase the bacterial burdens at 24 h postinfection. Thereafter, CAPs-exposed animals exhibited significantly lower bacterial burdens.

In another set of experiments, Zelokoff et al. (2003) evaluated the effects of CAPs exposure in rats following a single 5 h exposure to IT instilled Streptococcus pneumoniae. CAPs exposure significantly reduced the percentages of lavageable PMN 24 h following CAPs exposure and remained well below the match counterparts for up to 3 days. Lavageable PAM was significantly increased in the CAPs exposed animals. CAPs exposure reduced the levels of TNFα, IL-1, and IL-6. The bacterial burden reduced in both exposed groups over time, however, CAPs exposed animals had a significantly greater burden after 24 h than did control rats. Levels of lymphocytes and monocytes were unaffected by CAPs exposure.

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

To establish the temporal relationship between pulmonary injury, increased plasma fibrinogen, and changes in peripheral lymphocytes, Kodavanti et al. (2002) exposed spontaneously hypertensive (SH) and Wistar-Kyoto (WKY) rats to ROFA using both intratracheal and inhalation exposure (acute and long-term) scenarios. Increases in plasma fibrinogen and decreases in circulating white blood cells were found during the acute phase responses to ROFA exposure and were temporally associated with acute, but not long-term, lung injury. A bolus intratracheal instillation of ROFA increased plasma fibrinogen in both SH and WKY rats; whereas the increase was evident only in SH rats after acute ROFA inhalation. The increased fibrinogen in SH rats was associated with greater pulmonary injury and inflammation than was found in the WKY rats.

Nemmar et al. (2002) investigated the effect of ultrafine (60 nm) polystyrene particles on thrombus formation in a hamster model after IT administration of unmodified, carboxylate-polystyrene, or amine-polystyrene particles. Unmodified and carboxylate-polystyrene particles (5 mg/kg) did not modify significantly the intensity of thrombosis formed. In contrast the administration of 5 mg/kg amine-polystyrene particles significantly enhanced thrombosis formation. The authors concluded that the presence of ultrafine particles in the circulation may affect hemostasis and that this phenomenon is dependent on the surface properties of the particles.

Suwa et al. (2002) studied the effect of PM_{10} on the progression of atherosclerosis in rabbits. They exposed Watanabe heritable hyperlipidemic rabbits to PM_{10} (n = 10) or vehicle (n = 6) for four weeks, and both measured bone marrow stimulation and used quantitative histologic methods to determine the morphologic features of the atherosclerotic lesions. Exposure to PM_{10} caused an increase in circulating polymorphonuclear leukocytes (PMN) band cell counts and an increase in the size of the bone marrow mitotic pool of PMNs. Exposure to PM_{10} also caused progression of atherosclerotic lesions toward a more advanced phenotype. The volume fraction (vol/vol) of the coronary atherosclerotic lesions was increased by PM_{10} exposure. The vol/vol of atherosclerotic lesions correlated with the number of alveolar macrophages that phagocytosed PM_{10}. Exposure to PM_{10} also caused an increase in plaque cell turnover and extracellular lipid pools in coronary and aortic lesions, as well as in the total amount of lipids in aortic lesions.

In summary, controlled laboratory animal studies, to date, have provided evidence indicating that high concentrations of inhaled or instilled particles can have systemic, especially cardiovascular, effects. In the case of MCT rats, these effects can be lethal. Controlled human exposure studies also have shown that ambient levels of inhaled PM can produce some biochemical and cellular changes in the blood. Although some of these biochemical changes have been used as clinical "markers" for cardiovascular diseases, the causal relationship between these changes and the potential life-threatening diseases remains to be established. Understanding the pathways by which very small concentrations of inhaled ambient PM can produce systemic, life-threatening changes also is far from clear. Among the hypotheses that have been proposed to account for the nonpulmonary effects of PM are activation of neural reflexes, cytokine effects on heart tissue (Killingsworth et al., 1997), alterations in coagulability

(Seaton et al., 1995; Sjögren, 1997), 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 further such mechanistic hypotheses generated to date, as well as those that are likely to be proposed in the future.

7.4 PARTICULATE MATTER TOXICITY AND PATHOPHYSIOLOGY: IN VITRO EXPOSURES

7.4.1 Introduction

Toxicological studies play an integral role in determining the biological plausibility for the health effects associated with ambient PM exposure. At the time of 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) little was known about potential mechanisms that could explain the morbidity and mortality observed in populations exposed to PM. One of the difficulties in trying to sort out possible mechanisms is the nature of particles themselves. Ambient PM has diverse physicochemical properties (Table 7-8) ranging from the physical characteristics of the particle to the chemical components in or on the surface of the particle. Any one of these properties could change at any time in the ambient exposure atmosphere, making it hard to replicate the actual properties in a controlled experiment. As a result, controlled exposure studies as yet have not been able to unequivocally determine the particle properties and the specific mechanisms by which ambient PM may affect biological systems. Despite these underlying difficulties, a number of toxicological studies have become available since 1996 to help explain how ambient particles may exert toxic effects on the cardiovascular and respiratory systems. The following section discusses the more recently published studies that provide an approach toward identifying potential mechanisms by which PM mediates health effects. The remaining sections discuss potential mechanisms in relation to PM characteristics based on these available data.

7.4.2 Experimental Exposure Data

In vitro exposure is a useful technique to provide information on potential hazardous PM constituents and mechanisms of PM injury, especially when only limited quantities of the test

TABLE 7-8. 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 • semivolatile organics • metals (Fe, Cd, Co, Cu, Mn, Ni, Pb, Ti, V, Zn) • biologicals (e.g., pollen, microbes) • sulfates • nitrates • pesticides

material are available. In addition, in vitro exposure allows the examination of the response to particles in only one or two cell types. Respiratory epithelial cells that line the airway lumen are the initial targets of airborne pollutants. These cells have been featured in numerous studies involving airborne pollutants and show inflammatory responses similar to that of human primary epithelial cultures. Limitations of in vitro studies include difficulty in extrapolating dose-response relationships and from in vitro to in vivo biological response and mechanistic extrapolations. Besides alterations in physiochemcial characteristics of PM because of the collection and resuspension processes, these exposure conditions do not simulate the air-cell interface that actually exists within the lungs, and, thus, the exact dosage delivered to target cells in vivo is not known. Furthermore, unless an in vitro exposure system that is capable of delivering particles uniformly to monolayers of airway epithelial cells cultured in an air-liquid interface system is used (Chen et al., 1993), conventional incubation systems alter the microenvironment surrounding the cells and may alter the mechanisms of cellular injury induced by these agents.

Doses delivered in vitro, like intratracheal administration, are very high on a cellular basis, making it very difficult to extrapolate to in vivo exposure conditions. It would be useful if in vitro studies included, in addition to the high doses, doses comparable to environmental doses predicted to occur under in vivo conditions at the cellular level. Even with these limitations, in vitro studies do provide an approach to identify potential cellular and molecular mechanisms by which PM mediates health effects. These mechanisms can then be evaluated in vivo. In vitro studies published since the 1996 PM AQCD was completed are summarized in Table 7-9.

TABLE 7-9. IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human bronchial epithelial cells, asthmatic (ASTH) nonasthmatic (NONA)	DPM		10-100 µg/mL	0.4 µm	2, 4, 6, 24 h	DPM caused no gross cellular damage. Ciliary beat frequency was attentuated at all doses. DPM caused IL-8 release at 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		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	2.5×10^5 cells/mL	Urban and DPM: 12, 27, 111, 333, or 1000 µg/mL SiO_2 and TiO_2: 4, 12, 35, or 167 µg/mL Fe_2O_3: 1:1, 3:1; 10:1 particles/cell ratio	Urban particles: 0.3-0.4 µm DPM: 0.3 µm ROFA: 0.5 µm 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		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)		10 µg/cm^2	< 10 µm	24 h	PM_{10} stimulated alveolar macrophages to induce up-regulation of PDGF ∝ 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		0, 5, 50, or 200 µg/mL (actual dose delivered 1.6 – 60 µg/cm^2)	< 10 µm	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human erythrocytes; RAW 264.7 cells	$PM_{10-2.5}$; $PM_{2.5}$ from Rome, Italy	1×10^6 cells/mL	50 ± 45 µg/m^3 31 ± 24 µg/m^3 19 ± 20 µg/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		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	1×10^6 cells/mL	50 to 200 µg/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	3×10^4 cells/cm^2	5, 10, or 20 µg/cm^2	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		5, 10, or 20 µg/cm^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	1×10^4 cells/mL	5.3, 10.6, 21.2, 42.5, 85, 340 µg residue/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 (340 µg) when stimulated with PMA; 50% increase in LDH; disintegration of plasma membrane.	Fabiani et al. (1997)
BEAS-2B	Provo PM_{10} extract		125, 250, 500 µg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat AM	ROFA, iron sulfate, nickel sulfate, vanadyl sulfate Latex particles with metal complexed on the surface	0.5 – 1.0 × 10^6 cells/mL	0.01–1.0 mg/mL	3.6 µm MMAD	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		5, 50, 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		100 µg/mL	3.6 µm	5 min – 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		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		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	0.5 × 10^6 cells/mL	ROFA: 0, 25, 50, 100, or 200 µg/mL CAPS: 1:15, 1:10, 1:20 (described as 4, 10, 20 µg/mL)	CAPs: 0.1–2.5 µm (from Harvard concentrator) TiO_2: 1 µm	30 min incubation, analysis immediately following	Dose-dependent increase in AM oxidant stress with both ROFA and 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	0.5 × 10^6 cells/mL	ROFA: 25, 50, 100, 200 µg/mL CAPS: 38 – 180 µg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
AMs from female CD rats	Vanadyl chloride sodium metavanadate	$2 – 2.5 \times 10^6$ cells/mL	10-1000 µM metavanadate	N/A	30 min	Metavanadate caused increased production of ROS. The LOEL was 50 µM.	Grabowski et al. (1999)
Human PMN	Aqueous and organic extracts of TSP in Dusseldorf and Duisburg, Germany	1×10^6 cells/mL	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	1×10^6 cells/mL	0, 25, 100, or 200 µg/mL	Volume median diameter: ROFA 1.1 µm #1648: 1.4 µm #1649: 1.1 µm 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	$2 – 5 \times 10^5$ cells/cm^2	6.25, 12.5, 25, and 50 µg/cm^2	N/A	4, 8, and 24 h	ROFA was the most toxic particle, enhancing mucin secretion and causing toxicity, assessed by LDH release.	Jiang et al. (2000)
BEAS-2B	TSP collected in Provo	2×10^5 cells/mL	TSP filter samples (36.5 mg/mL) agitated in deionized H_2O_2 for 96 h, centrifuged at 1200 g for 30 min, lyophylized and resuspended in deionized H_2O_2 or saline	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human lung mucoepidermoid carcinoma cell line, NCI-H292	ROFA	1×10^6 cells/mL	10, 30, 100 µg/mL	N/A	1 and 24 h	Epithelial cells secreted increased mucin and lysozyme; effect time- and concentration-dependent; caused by V-rich fraction (18.8%).	Longphre et al. (2000)
BEAS-2B	ROFA	5×10^6 cells/mL	0, 0.5, or 2.0 mg in 10 mL	1.95 µm	1 h	ROFA induced production of acetaldehyde in dose-dependant fashion.	Madden et al. (1999)
Male (Wistar) rat lung macrophages	Urban dust SRM 1649, TiO_2, quartz	2×10^5 cells/mL	0-100 µg/mL	0.3 – 0.6 µm	18 h	Cytotoxicity ranking was quartz > SRM 1649 > TiO_2, based on cellular ATP decrease and LDH, acid phosphatase, and β-glucuronidase release.	Nadeau et al. (1996)
Human blood monocytes and neutrophils (PMN)	Ambient air particles, carbon black, oil fly ash, coal fly ash	2×10^5 cells/ 0.2 mL	100 µg 50, 100, 150, 200 µg	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)
BEAS-2B	ROFA		0, 6, 12, 25, or 50 µg/mL	1.96 µm	1 to 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)
BEAS-2B	ROFA		2, 20, or 60 µg/cm^2	1.96 µm	2 or 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)
BEAS-2B	ROFA Synthetic ROFA (soluble Ni, Fe, and V)		ROFA: 0–200 µg/mL Synthetic ROFA (100 µg/mL): Ni, 64 µM Fe, 63 µM V, 370 mM	ROFA: 1.96 µm Synthetic ROFA: N/A (soluble)	5 min to 24 h	Tyrosine phosphatase activity, which was known to be inhibited by vanadium ions, was markedly diminished after ROFA treatment; ROFA exposure induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in cells.	Samet et al. (1997)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human airway epithelium-derived cell lines BEAS-2B	Particle components As, Cr, Cu, Fe, Ni, V, and Zn		500 µM of As, F, Cr (III), Cu, V, Zn	N/A (soluble)	20 min and 6 and 24 h	Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in cells; activity assays confirmed marked activation of ERK, JNK, and P38 in cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK under these conditions; the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in cells treated with As, Cr, Cu, V, and Zn; acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in cells.	Samet et al. (1998)
A549 ØX174 RFI DNA	Urban particles: SRM 1648, St. Louis SRM 1649, Washington, DC	20,000 cells/cm^2	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)
Human AMs	Provo PM_{10} extract	2×10^5 cells/mL	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_20 soluble(s) and insoluble(is)	2×10^7 cells/mL	100 µg/mL	$PM_{2.5}$ $PM_{10\text{-}2.5}$	24 h	Increased cytokine production (IL-6, TNFα, MCP-1); $isPM_{10} > sPM_{10} > isPM_{2.5}$; $sPM_{2.5}$ was inactive; endotoxin was partially responsible.	Soukup and Becker (2001)
Rat (Wistar) AM RAM cells (a rat AM cell line)	TiO_2	1×10^6 cells/mL	20, 50, or 80 µg/mL	N/A	4 h	Opsonization of TiO_2 with surfactant components resulted in a modest 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	2.5×10^5 cells/mL	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-9 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
A549	TiO_2, Fe_2O_3, CAP, and the fibrogenic particle α-quartz	3×10^5 cells/mL	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	$TiO_2 > Fe_2O_3 >$ α-quartz > CAP in particle binding; binding of particle was found to be calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was calcium-independent; scavenger receptor, mediate particulate binding; α-quartz, 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	1×10^6 cells/mL	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.	1×10^4 cells/100 µL		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	ROFA Birmingham, AL. 188 mg/g of VO		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. (1999a)
NHBE BEAS-2B	Utah Valley PM_{10} extract		50, 100, 200 µg/mL	PM_{10}	24 h	Dose-dependent increase in expression of IL-8 produced 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; NHBE = Normal human bronchial epithelial; A549 = Human lung epithelial cell line.
[b]DEF = Deferoxamine
ROFA = Residual oil fly ash
UAP = Urban air particulates
TSP = Total suspended particles
CAP = Concentrated air particles
DOFA = Domestic oil fly ash
VO = Vanadate oxide
CFA = Coal fly ash
PFA = Pulverized fuel ash
TiO_2 = Titanium oxide

DRAFT-DO NOT QUOTE OR CITE

7.4.2.1 Ambient Particles

Several studies have exposed airway epithelial cells, alveolar macrophages, or blood monocytes and erythrocytes to aqueous extracts of ambient PM to investigate cellular processes such as oxidant generation and cytokine production that may contribute to the pathophysiological response seen in vivo. Among the ambient PM being examined were samples collected from Boston, MA (Goldsmith et al., 1998); North Provo, UT (Ghio et al., 1999a,b); St. Louis, MO (SRM 1648, Dong et al., 1996; Becker and Soukup, 1998); Washington, DC (SRM 1649, Becker and Soukup, 1998); Ottawa, Canada (EHC-93, Becker and Soukup, 1998); Dusseldorf and Duisburg, Germany (Hitzfeld et al., 1997), Mexico City (Bonner et al., 1998), Terni, Italy (Fabiani et al., 1997); and Rome, Italy (Diociaiuti et al., 2001). In any in vitro study, however, potential exists for contamination of ambient PM by biologic material during collection on filters. Endotoxin contamination, in particular, can occur at any time in the manufacture of the filter media or during handling of the filter samples before, during, and after the particle collection process. This potential inadvertent contamination of filter samples can make extrapolation of the study results difficult, although careful handling, characterization, and controls can eliminate these concerns.

Because soluble metals of ambient surrogates like ROFA have been associated with biological effect and toxicity, several studies have investigated whether the soluble components of ambient PM may have the same biological activities. Extracts of ambient PM samples collected from North Provo, UT, (during 1981 and 1982) were used to test whether the soluble components or ionizable metals, which accounted for approximately 0.1% of the mass, are 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 incubated overnight in cell culture, only the former particles caused an immediate oxidative response in AMs. Host defense effects were attributed to apoptosis which was most evident in particles collected before plant closure. Interpretation of loss of these effects by chelation removal of the metals was complicated by the observed differences in apoptosis despite similar metal contents of ambient PM collected during the steel mill operation.

Wu et al. (2001) investigated the intracellular signaling mechanisms for the pulmonary responses to Utah Valley PM extracts. Human primary airway epithelial cells were exposed to aqueous extracts of PM collected from the year before, during, and after the steel mill closure in Utah Valley. Transfection with kinase-deficient extracellular signal-regulated kinase (ERK) constructs partially blocked the PM-induced interleukin (IL)-8 promoter reporter activity. The

mitogen-activated protein kinase/ERK kinase (MEK) activity inhibitor PD-98059 significantly abolished IL-8 released in response to the PM, as did the epidermal growth factor (EGF) receptor kinase inhibitor AG-1478. Western blotting showed that the PM-induced phosphorylation of EGF receptor tyrosine, MEK1/2, and ERK1/2 could be ablated with AG-1478 or PD-98059. The results indicate that the potency of Utah Valley PM collected during plant closure was lower than that collected while the steel mill was in operation and imply that Utah Valley PM can induce IL-8 expression partially through the activation of the EGF receptor signaling.

There are regional as well as daily variations in the composition of ambient PM and, hence, its biological activities. For example, concentrated ambient PM (CAP, from Boston urban air) has substantial day-to-day variability in its composition and oxidant effects (Goldsmith et al., 1998). Similar to Utah PM, the water-soluble component of Boston CAPs significantly increased AM oxidant production and inflammatory cytokine (MIP2 and TNFα) production over negative control values. These effects can be blocked by metal chelators or antioxidants. The regional difference in biological activity of ambient PM has been shown by Becker and Soukup (1998). The oxidant generation, phagocytosis, as well as the expressions of receptors important for phagocytosis in human alveolar macrophage and blood monocyte were reduced significantly by PM exposure.

Becker and Soukup (1998) and others (Dong et al., 1996, Becker et al., 1996) have suggested that the biological activity of the ambient PM may result from the presence of endotoxin on the particles rather than metal-associated oxidant generation. Using the same urban particles (SRM 1648), cytokine production (TNF-α, IL-1, Il-6, CINC, and MIP-2) was increased in macrophages following treatment with 50 to 200 μg/mL of urban PM (Dong et al., 1996). The urban particle-induced TNF-α secretion was abrogated completely by treatment with polymyxin B, an antibiotic that blocks LPS-associated activities, but not with antioxidants.

The involvement of endotoxin, at least partially, in PM induced biological effects was supported more recently by Bonner et al. (1998) and Soukup and Becker (2001). Urban PM_{10} collected from north, south, and central regions of Mexico City was used with SD rat AM to examine PM effects on platelet-derived growth factor (PDGF) receptors on lung myofibroblasts (Bonner et al., 1998). Mexico City PM_{10} (but not volcanic ash) stimulated secretion of upregulatory factors for the PDGF α receptor, possibly via IL-1β. In the presence of an

endotoxin-neutralizing protein, the Mexico City PM_{10} effect on PDGF was blocked partially, suggesting that LPS was responsible partially for the effect of the PM_{10} on macrophages. In addition, both LPS and vanadium (both present in the PM_{10}) acted directly on lung myofibroblasts. However, the V levels in Mexico City PM_{10} were probably not high enough to exert an independent effect. The authors concluded that PM_{10} exposure could lead to airway remodeling by enhancing myofibroblast replication and chemotaxis.

Soukup and Becker (2001) collected fresh $PM_{2.5}$ and $PM_{10-2.5}$ from the ambient air of Chapel Hill, NC, and compared the activity of these two particle size fractions. Both water soluble and insoluble components were assessed for cytokine production, inhibition of phagocytosis, and induction of apoptosis. The most potent fraction was the insoluble $PM_{10-2.5}$ thus suggesting the importance of the coarse fraction in the investigation of ambient PM's health effects. Endotoxin was responsible for much of the cytokine production, while inhibition of phagocytosis was induced by other moieties in the coarse material. None of the activities were inhibited by the metal chelator deferoxamine.

The effects of water soluble as well as organic components (extracted in dichloromethane) of ambient PM were investigated by exposing human PMN to PM extracts (Hitzfeld et al., 1997). PM was collected with high-volume samplers in two German cities, Dusseldorf and Duisburg; these sites have high traffic and high industrial emissions, respectively. Organic, but not aqueous, extracts of PM alone significantly stimulated production and release of ROS in resting human PMN. The effects of the PM extracts were inhibited by SOD, catalase, and sodium azide (NaN_3). Similarly, the organic fraction (extractable by acetone) of ambient PM from Terni, Italy, was shown to produce cytotoxicity, superoxide release in response to PMA and zymosan in peripheral monocytes (Fabiani et al., 1997).

Diociaiuti et al. (2001) compared the in vitro toxicity of coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$) particulate matter, collected in an urban area of Rome. The in vitro toxicity assays used included human red blood cell hemolysis, cell viability, and nitric oxide (NO) release in the RAW 264.7 macrophage cell line. There was a dose-dependent hemolysis in human erythrocytes when they were incubated with fine and coarse particles. The hemolytic potential was greater for the fine particles than for the coarse particles in equal mass concentration. However, when data were expressed in terms of PM surface area per volume of suspension, the hemolytic activity of the fine fraction was equal to the coarse fraction. This result suggested that the oxidative stress

induced by PM on the cell membranes could be due mainly to the interaction between the particle surfaces and the cell membranes. Although RAW 264.7 cells challenged with fine and coarse particles showed decreased viability and an increased release of NO, a key inflammatory mediator, both effects were not dose-dependent in the tested concentration range. The fine particles were the most effective in inducing these effects when the data were expressed as mass concentration or as surface area per unit volume. The authors concluded that these differences in biological activity were due to the differing physicochemical nature of the particles.

7.4.2.2 Comparison of Ambient and Combustion-Related Surrogate Particles

In vitro toxicology studies utilizing alveolar macrophages as target cells (Imrich et al., 2000; Long et al., 2001; Ning et al., 2000; Mukae et al., 2000, 2001; Van Eeden et al., 2001) have found that urban air particles are much more potent for inducing cellular responses than individual combustion particles such as diesel and ROFA. Similar to the results described above in Section 7.5.2.1, these studies also show that when cytokine responses are measured, LPS/endotoxin is found to be responsible for most of the activity. Metals, on the other hand, do not seem to affect cytokine production, as confirmed by studies showing that ROFA does not induce macrophage cytokine production. These results are important because LPS is an important component associated with both coarse and fine particles (Menetrez et al., 2001). In fact, in one study (Long et al., 2001), cytokine responses in the alveolar macrophages were correlated with LPS content and more LPS was found associated with indoor $PM_{2.5}$ than outdoor $PM_{2.5}$.

Imrich et al. (2000) found that when mice alveolar macrophages were stimulated with 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 prostaglandin H synthase-2 (PHS-2) as well as mRNA coded for this enzyme. In contrast, expression of the PHS1 form of the enzyme was not affected by ROFA treatment of airway epithelial cells. These investigators further demonstrated that 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 fraction and were mimicked by V-containing solutions but not iron or nickel solutions (Samet et al., 1997).

ROFA also stimulates respiratory cells to secrete inflammatory cytokines such as IL-6, IL-8, and TNF. Normal human bronchial epithelial (NHBE) cells exposed to ROFA produced significant amounts of IL-8, IL-6, and TNF, as well as mRNAs coding for these cytokines (Carter et al., 1997). Increases in cytokine production were dose-dependent. The cytokine

production was inhibited by the addition of metal chelator, DEF, or the free radical scavenger dimethylthiourea (DMTU). Similar to the data of Samet et al. (1997), V but not Fe or Ni compounds were responsible for these effects. Cytotoxicity, decreased cellular glutathione levels in primary cultures of rat tracheal epithelial (RTE) cells exposed to suspensions of ROFA indicated that respiratory cells exposed to ROFA were under oxidative stress. Treatment with buthionine sulfoxamine (an inhibitor of γ-glutamyl cysteine synthetase) augmented ROFA-induced cytotoxicity; whereas treatment with DMTU inhibited ROFA-induced cytoxicity further suggested that ROFA-induced cell injury may be mediated by hydroxyl-radical-like reactive oxygen species (ROS) (Dye et al., 1997). Using BEAS-2B cells, a time- and dose-dependent increase in IL-6 mRNA induced by ROFA was shown to be preceded by the activation of nuclear proteins, for example, nuclear factor-κB (NF-κB) (Quay et al., 1998). Taken together, ROFA exposure increases oxidative stress, perturbs protein tyrosine phosphate homeostasis, activates NF-κB, and up-regulates inflammatory cytokine and prostaglandin synthesis and secretion to produce lung injury.

Stringer and Kobzik (1998) observed that "primed" lung epithelial cells exhibited enhanced cytokine responses to PM. Compared to normal cells, exposure of tumor necrosis factor (TNF)-α-primed A549 cells to ROFA or α -quartz caused increased IL-8 production in a concentration-dependent manner for particle concentrations ranging from 0-200 μg/mL. Addition of the antioxidant N-acetylcysteine (NAC) (1.0 mM) decreased ROFA and α -quartz-mediated IL-8 production by approximately 50% in both normal and TNF-α-primed A549 cells. Exposure of A549 cells to ROFA caused an increase in oxidant levels that could be inhibited by NAC. These data suggest that (1) lung epithelial cells primed by inflammatory mediators show increased cytokine production after exposure to PM and (2) oxidant stress is an important mechanism for this response.

In summary, exposure of lung epithelial cells to ambient PM or ROFA leads to increased production of cytokines and the effects may be mediated, at least in part, through production of ROS. Day-to-day variations in the components of PM, such as soluble transition metals (which may be critical to eliciting the response) are suggested. The involvement of organic components in ambient PM was also suggested by some studies.

7.4.2.3 Mutagenicity

The majority of recent PM research has focused on the acute cardiopulmonary effects which have been documented to occur following episodic exposure to ambient PM. However, epidemiologic investigations have recently linked chronic exposure to ambient PM not only to increases in long term cardiopulmonary mortality but also to lung cancer effects (Pope, 2002). Also, a limited number of recent studies have examined the mutagenic potential of ambient PM and, in general, they have shown some degree of evidence that appears to support the biologic plausibility of the long-term lung cancer effects.

These in vitro studies, discussed in Table 7-10, have focused on the ability of the organic fraction of ambient PM to induce mutagenic effects in mammalian cell lines and bacteria. The organic fractions produced increase mutations (revertants) in the Ames assay (Bunger, 2000) as well as sister chromatid exchanges in mammalian cells (Hornberg, 1996, 1998). Seemayer and colleagues (1998) also observed increases in SV40 transformation of hamster kidney cells treated with extracts of ambient PM collected with a high volume sampler. Investigators have also compared the mutagenic potential of the combustion products of high and low sulfur content diesel fuel with plant derived fuels. In the Ames assay, the number of revertants was significantly elevated in bacteria treated with high versus low sulfur diesel fuel. Moreover, the high sulfur fuel caused more mutations than the plant-derived fuels.

Although each of the above studies demonstrates the mutagenic potential of ambient PM and fuel combustion products, these in vitro studies are generally lacking in details regarding the dose of PM extract delivered to the cells in vitro. In general, equal volumes of air or amounts of time were sampled, but little to no characterization of the amount of PM mass or size were determined. Thus, the relevance of these mutagenicity studies is still quite limited in terms of substantiating the biologic plausibility of, or elucidating potential mechanisms underlying, the reported associations between long-term exposure to PM and increases in lung cancer.

7.4.3 Potential Cellular and Molecular Mechanisms

7.4.3.1 Reactive Oxygen Species

Ambient particulate matter contains transition metals, such as iron (most abundant), copper, nickel, zinc, vanadium, and cobalt. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen

TABLE 7-10. MUTAGENIC/CARCINOGENIC EFFECTS OF PARTICULATE MATTER

Particle	Species, Gender, Strain Age, or Body Weight	Exposure Technique	Mass Concentration (μg/mL) or (μg/m^3)	Particle Characteristics Size (μm); μ_g	Exposure Duration	Adverse Effects of Particles on Mammalian Cells or Bacteria	Reference
Ambient PM	Cultured tracheal epithelial cells from Hamster, Syrian golden, young	in vitro	Not given	Dichloromethane extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 48 hours.	Dose-related increases in sister chromatid exchanges were observed.	Hornberg (1996)
Ambient PM_{10} and $PM_{2.5}$ collected in industrial and rural regions	Human bronchioepithelial cell line (BEAS-2B)	in vitro	Not given in μg/mL	Dichloromethane extraction of coarse (PM_{10}) and fine ($PM_{2.5}$) fractions.	Dilutions of extracted organic phase of size-segregated particles incubated with cells for 72 hours.	Significant increases in sister chromatid exchanges were greater in $PM_{2.5}$ from all sampling sites. Extraction phase of coarse particles produced fewer sister chromatid exchanges than did the fine particles.	Hornberg (1998)
Ambient particles and particles from diesel exhaust, rubber and metal industries, and biologic sources (poultry/swine farming)	Liver tumor cell line (HEPA1c1c7)	in vitro	6 to 226 μg/mL	Aqueous and organic extraction of particles collected with high volume samplers.	Not given.	Inhibition of gap-junctional intercellular communication was significant only in cells treated with aqueous extract of diesel, compost, or rubber particles.	Alink (1998)
Ambient PM	Kidney cells from hamster, Syrian golden, 8-10 weeks old	in vitro	Not given	Dichloromethane extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 18 hours followed by infection with simian virus SV-40.	Significantly greater SV-40-induced transformation of hamster kidney cells pre-treated with organic extractions of urban particles.	Seemayer and Hornberg (1998)
Diesel exhaust particles	Ames assay with and without activation	in vitro	Not given	Dichloromethane extraction of particles collected from diesel engine run with diesel fuels with low or high sulfur and 2 plant oil fuels.	48 hours incubation with TA98 and TA100 strains.	Revertants were 2 to 10-fold higher with high sulfur diesel fuel particles.	Bunger (2000)
Ambient PM	Cultured hepatoma cells	in vitro	Not given	Acetone/dichloromethane extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 6 or 48 hours.	Extracts of ambient PM both upwind and downwind of highway have genotoxic effects although PAH content was greater in downwind samples.	Hamers (2000)

DRAFT-DO NOT QUOTE OR CITE

species (ROS). These reactions can be demonstrated by the iron-catalyzed Haber-Weiss reactions that follow.

$$\text{Reductant}^{n} + \text{Fe(III)} \rightarrow \text{Reductant}^{n+1} + \text{Fe(II)} \quad (1)$$

$$\text{Fe(II)} + O_2^- \rightarrow \text{Fe(III)} + O_2^- \quad (2)$$

$$HO_2^- + O_2^- + H^+ \rightarrow O_2 + H_2O_2 \quad (3)$$

$$\text{Fe(II)} + H_2O_2 \rightarrow \text{Fe(III)} + {}^{\bullet}OH + HO^- \text{(Fenton Reaction)} \quad (4)$$

Iron will continue to participate in the redox cycle in the above reactions as long as there is sufficient O_2 or H_2O_2 and reductants.

Soluble metals from inhaled PM dissolved into the fluid lining of the airway lumen can react directly with biological molecules (acting as a reductant in the above reactions) to produce ROS. For example, ascorbic acid in the human lung epithelial lining fluid can react with Fe(III) from inhaled PM to cause single strand breaks in supercoiled plasmid DNA, ϕX174 RFI (Smith and Aust, 1997). The DNA damage caused by a PM_{10} suspension can be inhibited by mannitol, an hydroxyl radical scavenger, further confirming the involvement of free radicals in these reactions (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997). Because the clear supernatant of the centrifuged PM_{10} suspension contained all of the suspension activity, the free radical activity is derived either from a fraction that is not centrifugable (10 min at 13,000 rpm on a bench centrifuge) or the radical generating system is released into solution (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997).

In addition to measuring the interactions of ROS and biomolecules directly, the role of ROS in PM-induced lung injury also can be assessed by measuring the electron spin resonance (ESR) spectrum of radical adducts or fluorescent intensity of dichlorofluorescin (DCFH), an intracellular dye that fluoresces on oxidation by ROS. Alternatively, ROS can be inhibited using free radical scavengers, such as dimethylthiourea (DMTU); antioxidants, such as glutathione or N-acetylcysteine (NAC); or antioxidant enzymes, such as superoxide dismutase (SOD). The diminished response to PM after treatment with these antioxidants may indicate the involvement

of ROS; however, some antioxidants (e.g., thiol-containing) can interact with metal ions directly.

As described earlier, Kadiiska et al. (1997) used the ESR spectra of 4-POBN [α-(4-pyridyl 1-oxide)-N-tert-butylnitrone] adducts to measure ROS in rats instilled with ROFA and demonstrated the association between ROS production within the lung and soluble metals in ROFA. Using DMTU to inhibit ROS production, Dye et al. (1997) had shown that systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. Goldsmith et al. (1998), as described earlier, showed that ROFA and CAPs caused increases in ROS production in AMs. The water-soluble component of both CAPs and ROFA significantly increased AM oxidant production over negative control values. In addition, increased PM-induced cytokine production was inhibited by NAC. Li et al. (1996, 1997) instilled rats with PM_{10} particles (collected on filters from an Edinburgh, Scotland, monitoring station). Six hours after intratracheal instillation of PM_{10}, they observed a decrease in glutathione (GSH) levels in the BAL fluid. Although this study does not describe the composition of the PM_{10}, the authors suggest that changes in GSH, an important lung antioxidant, support the contention that the free radical activity of PM_{10} is responsible for its biological activity in vivo.

In addition to ROS generated directly by PM, resident or newly recruited AMs or PMNs also are capable of producing these reactive species on stimulation. The ROS produced during the oxidative burst can be measured using a chemiluminescence (CL) assay. With this assay, AM CL signals in vitro have been shown to be greatest with ROFA containing primarily soluble V and were less with ROFA containing Ni plus V (Kodavanti et al., 1998a). As described earlier, exposures to Dusseldorf and Duisburg PM increased the resting ROS production in PMNs, which could be inhibited by SOD, catalase, and sodium azide (Hitzfeld et al., 1997). Stringer and Kobzik (1998) showed that addition of NAC (1.0 mM) decreased ROFA-mediated IL-8 production by approximately 50% in normal and TNF-α-primed A549 cells. In addition, exposures of A549 cells to ROFA caused a substantial (and NAC inhibitable) increase in oxidant levels as measured by DCFH oxidation. In human AMs, Becker et al. (1996) found a CL response for ROFA, but not urban air particles (Ottawa and Dusseldorf) or volcanic ash.

Metal compounds of PM are the most probable species capable of catalyzing ROS generation on exposure to PM. To determine elemental content and solubility in relation to their ability to generate ROS, PMN or monocytes were exposed to a wide range of ambient air

particles from divergent sources (one natural dust, two types of oil fly ash, two types of coal fly ash, five different ambient air samples, and one carbon black sample), and CL production was measured over a 20-min period postexposure (Prahalad et al., 1999). Percent of sample mass accounted for by XRF detectable elements was 1.2% (carbon black); 22 to 29% (natural dust and ambient air particles); 13 to 22% (oil fly ash particles); and 28 to 49% (coal fly ash particles). The major proportion of elements in most of these particles were aluminosilicates and insoluble iron, except oil derived fly ash particles in which soluble vanadium and nickel were in highest concentration, consistent with particle acidity as measured in the supernatants. All particles induced CL response in cells, except carbon black. The CL response of PMNs in general increased with all washed particles, with oil fly ash and one urban air particle showing statistical differences between deionized water washed and unwashed particles. These CL activities were significantly correlated with the insoluble Si, Fe, Mn, Ti, and Co content of the particles. No relationship was found between CL and soluble transition metals such as V, Cr, Ni, and Cu. Pretreatment of the particles with a metal ion chelator, deferoxamine, did not affect CL activities. Particle sulfate content and acidity of the particle suspension did not correlate with CL activity.

Soluble metals can be mobilized into the epithelial cells or AMs to produce ROS intracellularly. Size-fractionated coal fly ash particles (2.5, 2.5 to 10, and < 10 μm) of bituminous b (Utah coal), c (Illinois coal), and lignite (Dakota coal) were used to compare the amount of iron mobilization in A549 cells and by citrate (1 mM) in cell-free suspensions (Smith et al., 1998). Iron was mobilized by citrate from all three size fractions of all three coal types. More iron, in Fe(III) form, was mobilized by citrate from the < 2.5-μm fraction than from the > 2.5-μm fractions. In addition, the amount of iron mobilized was dependent on the type of coal used to generate the fly ash (Utah coal > Illinois coal = Dakota coal) but was not related to the total amount of iron present in the particles. Ferritin (an iron storage protein) levels in A549 cells increased by as much as 12-fold in cells treated with coal fly ash (Utah coal > Illinois coal > Dakota coal). More ferritin was induced in cells treated with the < 2.5-μm fraction than with the > 2.5-μm fractions. Mossbauer spectroscopy of a fly ash sample showed that the bioavailable iron was assocated with the glassy aluminosilicate fraction of the particles (Ball et al., 2000). As with the bioavailability of iron, there was an inverse correlation between the production of IL-8 and fly ash particle size, with the Utah coal fly ash being the most potent.

Using ROFA and colloidal iron oxide, Ghio et al. (1997b; 1998a,b,c; 1999c; 2000c) have shown that exposures to these particles disrupted iron homeostasis and induced the production of ROS in vivo and in vitro. Treatment of animals or cells with metal-chelating agents such as DEF with an associated decrease in response has been used to infer the involvement of metal in PM-induced lung injury. Metal chelation by DEF (1 mM) caused significant inhibition of particulate-induced AM oxidant production, as measured using DCFH (Goldsmith et al., 1998). DEF treatment also reduced NF-κB activation and cytokine secretion in a human bronchial epithelial cell line (BEAS-2B cells) exposed to Provo PM (Kennedy et al., 1998). However, treatment of ROFA suspension with DEF was not effective in blocking leachable metal induced acute lung injury (Dreher et al., 1997). Dreher et al. (1997) indicated that DEF could chelate Fe(III) and V(II), but not Ni(II), suggesting that metal interactions played a significant role in ROFA-induced lung injury.

Other than Fe, several V compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of V, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5. However, metal components of fly ash have not been shown to consistently increase ROS production from bovine AM treated with combustion particles (Schlüter et al., 1995). For example, As(III), Ni(II), and Ce(III), which are major components of fly ash, had been shown to inhibit the secretion of superoxide anions (O_2^-) and hydrogen peroxide. In the same study, O_2^- were lowered by Mn(II) and Fe(II); whereas V(IV) increased O_2^- and H_2O_2. In contrast, Fe(III) increased O_2^- production, demonstrating that the oxidation state of metal may influence its oxidant generating properties. Other components of fly ash, such as Cd(II), Cr(III), and V(V), had no effects on ROS.

It is likely that a combination of several metals rather than a single metal in PM is responsible for the PM-induced cellular response. For example, V and Ni+V but not Fe or Ni alone (in saline with the final pH at 3.0) resulted in increased epithelial permeability, decreased cellular glutathione, cell detachment, and lytic cell injury in rat tracheal epithelial cells exposed to soluble salts of these metals at equivalent concentrations found in ROFA (Dye et al., 1999). Treatment of V-exposed cells with buthionine sulfoximine further increased cytotoxicity. Conversely, treatment with radical scavenger dimethyl thiourea inhibited the effects in a

dose-dependent manner. These results suggest that soluble metal or combinations of several metals in ROFA may be responsible for these effects.

Similar to combustion particles such as ROFA, the biological response to exposure to ambient PM also may be influenced by the metal content of the particles. Human subjects were instilled with 500 μg (in 20 mL sterile saline) of Utah Valley dust (UVD1, 2, 3, collected during 3 successive years) on the left segmental bronchus and on the right side with sterile saline as control. A second bronchoscopy was performed 24 hours post-instillation and phagocytic cells were obtained from the segmental bronchi on both sides. Alveolar macrophage from subjects instilled with UVD, obtained by bronchoaveolar lavage 24 h post-instillation, were incubated with fluoresceinated yeast (Saccharomyces cerevisiae) to assess their phagocytic ability. Although the same proportion of AMs were exposed to UVD phagocytized yeast, AMs exposed to UVD1, which were collected while a local steel mill was open, took up significantly less particles than AMs exposed to other extracts (UVD2 when the steel mill was closed and UVD3 when the plant reopened). AMs exposed to UVD1 also exhibited a small decrease in oxidant activity (using dihydrorhodamine-123, DHR). AMs from healthy volunteers were incubated in vitro with the various UVD extracts to assess whether similar effects on human AMs function could be observed to those seen following in vivo exposure. The percentage of AMs that engulfed yeast particles was significantly decreased by exposure to UVD1 at 100 μg/mL, but not at 25 μg/mL. However, the amount of particles engulfed was the same following exposure to all three UVD extracts. AMs also demonstrated increased oxidant stress (using chemiluminescence) after in vitro exposure to UVD1, and this effect was not abolished with pretreatment of the extract with the metal chelator deferoxamine. As with the AMs exposed to UVD in vivo, AM exposed to UVD in vitro had a decreased oxidant activity (DHR assay). UVD1 contains 61 times and 2 times the amount of Zn compared to UVD 2 and UVD3, respectively; whereas UVD3 contained 5 times more Fe than UVD1. Ni and V were present only in trace amounts. Using similarly extracted samples, Frampton et al. (1999) exposed BEAS-2B cells for 2 and 24 h. Similar results were observed for oxidant generation in these cells (i.e., UVD 2, which contains the lowest concentrations of soluble iron, copper, and zinc, produced the least response). Only UVD 3 produced cytotoxicity at a dose of 500 μg/mL. UVD 1 and 3, but not 2, induced expression of IL-6 and 8 in a dose-dependent fashion. Taken together, the above results showed that the biological response to ambient particle extracts is heavily dependent on the source and, hence, the chemical composition of PM.

7.4.3.2 Intracellular Signaling Mechanisms

In has been shown that the intracellular redox state of the cell modulates the activity of several transcription factors, including NF-κB, a critical step in the induction of a variety of proinflammatory cytokine and adhesion-molecule genes. NF-κB is a heterodimeric protein complex that in most cells resides in an inactive state in the cell cytoplasm by binding to inhibitory kappa B alpha (IκBα). On appropriate stimulation by cytokines or ROS, IκBα is phosphorylated and subsequently degraded by proteolysis. The dissociation of IκBα from NF-κB allows the latter to translocate into the nucleus and bind to appropriate sites in the DNA to initiate transcription of various genes. Two studies in vitro have shown the involvement of NF-κB in particulate-induced cytokine and intercellular adhesion molecule-1 (ICAM-1) production in human airway epithelial cells (BEAS-2B) (Quay et al., 1998; Kennedy et al., 1998). Cytokine secretion was preceded by activation of NF-κB and was reduced by treatment with antioxidants or metal chelators. These results suggest that metal-induced oxidative stress may play a significant role in the initiation phase of the inflammatory cascade following PM exposure.

A second well-characterized human transcription factor, AP-1, also responds to the intracellular ROS concentration. AP-1 exists in two forms, either in a homodimer of c-jun protein or a heterodimer consisting of c-jun and c-fos. Small amounts of AP-1 already exist in the cytoplasm in an inactive form, mainly as phosphorylated c-jun homodimer. Many different oxidative stress-inducing stimuli, such as UV light and IL-1, can activate AP-1. Exposure of rat lung epithelial cells to ambient PM in vitro resulted in increases in c-jun kinase activity, levels of phosphorylated c-jun immunoreactive protein, and transcriptional activation of AP-1-dependent gene expression (Timblin et al., 1998). This study 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 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.

Inhaled fine and coarse particles are trapped by impaction in the epithelial lining of the nasal and tracheal airways. Somatosensory neurons located in the dorsal root ganglia (DRG) innervate the upper thoracic region of the airways and extend their terminals over and between the epithelial lining of the lumen. Given this anatomical proximity, the sensory fibers and the tracheal epithelial cells that they innervate encounter inhaled pollutants, such as PM, early during inhalation. The differential responses of these cell types to PM derived from various sources (i.e., industrial, residential, volcanic) were examined with biophysical and immunological endpoints (Veronesi et al., 2002a). Although the majority of PM tested stimulated IL-6 release in both BEAS-2B epithelial cells and DRG neurons in a receptor-mediated fashion, the degree of these responses was markedly higher in sensory neurons. Epithelial cells are damaged or denuded in many common health disorders (e.g., asthma, viral infections), allowing PM particles to directly encounter the sensory terminals and their acid-sensitive receptors.

Another intracellular signaling pathway that could lead to diverse cellular responses such as cell growth, differentiation, proliferation, apoptosis, and stress responses to environmental stimuli, is the phosphorylation-dependent, mitogen-activated protein kinase (MAPK). Significant dose- and time-dependent increases in protein tyrosine phosphate levels have been seen in BEAS cells exposed to 100 μg/mL ROFA for periods ranging from 5 min to 24 h (Samet et al., 1997). In a subsequent study, the effects of As, Cr, Cu, Fe, Ni, V, and Zn on the MAPK, extracellular receptor kinase (ERK), c-jun N-terminal kinase (JNK), and P38 in BEAS cells were investigated (Samet et al., 1998). Arsenic, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells. Activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn; Cr and Cu exposure resulted in a relatively small activation of MAPK; whereas Fe and Ni did not activate MAPK. Similarly, the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn. The same acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells. All exposures were non-cytotoxic based on measurement of lactate dehydrogenase release and microscopic examination of trypan blue or propidium iodide exclusion (Samet et al., 1996). These data suggest that MAPK may mediate metal-induced expression of inflammatory proteins

in human bronchial epithelial cells. The ability of ROFA to induce activation of MAPKs in vivo was demonstrated by Silbajoris et al. (2000; see Table 7-3). In addition, Gercken et al. (1996) showed that the ROS production induced by PM was markedly decreased by the inhibition of protein kinase C as well as phospholipase A_2. Comparisons of in vitro and in vivo exposures of ROFA to airway epithelial cells requires consideration of in vivo dosimetry and ambient concentrations. Therefore, such extrapolations must be made with caution.

The major cellular response downstream of ROS and the cell signaling pathways described above is the production of inflammatory cytokines or other reactive mediators. In an effort to determine the contribution of cyclooxygenase to the pulmonary responses to ROFA exposure in vivo, Samet et al. (2000) intratracheally instilled Sprague-Dawley rats with ROFA (200 or 500 μg in 0.5 mL saline). These animals were pretreated ip with 1 mg/kg NS398, a specific prostaglandin H synthase 2 (COX2) inhibitor, 30 min prior to intratracheal exposure. At 12 h after intratracheal instillations, ip injections (1 mL of NS398 in 20% ethanol in saline) were repeated. ROFA treatment induced a marked increase in the level of PGE_2 recovered in the BAL fluid, which was effectively decreased by pretreating the animals with the COX2 inhibitor. Immunohistochemical analyses of rat airway showed concomitant expression of COX2 in the proximal airway epithelium of rats treated with soluble fraction of ROFA. This study further showed that, although COX2 products participated in ROFA induced lung inflammation, the COX metabolites are not involved in IL-6 expression nor the influx of PMN influx into the airway. However, the rationale for the use of intraperitoneal challenge was not elaborated.

The production of cytokines and mediators also has been shown to depend on the type of PM used in the experiments. A549 cells (a human airway epithelial cell line) were exposed in vitro to several particulate materials: carbon black (CB, Elftex-12, Cabot Corp.), diesel soot from two sources (ND from NIST, LD produced from General Motors LH 6.2 V8 engine at light duty cycle), ROFA (from the heat exchange section of the Boston Edison), OAA (Ottawa ambient air PM, EHC-93), SiO_2, and Ni_3S_2 at 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 100, 300, 1,000 $\mu g/cm^2$ for 18 h (Seagrave and Nikula, 2000). Endpoints included loss of adherence to tissue culture substratum as evaluated by crystal violet staining, cell death measured by lactate dehydrogenase release, release of interleukin-8 (IL-8) measured by enzyme-linked immunosorbent assay, mitotic fraction and apoptosis, and release of alkaline phosphatase measured by enzymatic activity using paranitrophenol phosphate. Results indicated that (1) SiO_2 and Ni_3S_2 caused dose dependent acute toxicity and apototic changes; (2) ROFA and ND were

acutely toxic only at the highest concentrations; (3) SiO_2 (30, 100, 300 μg/cm^2) and Ni_3S_2 (10, 30, 100, 300 μg/cm^2) increased IL-8 (three and eight times over the control, respectively) but suppressed IL-8 release at the highest concentration; (4) OAA and ROFA also induced IL-8 but to a lesser degree; and (5) both diesel soots suppressed IL-8 production. The authors speculated that the suppression of IL-8 release may contribute to increased respiratory disease as a result of decreased response to infectious agents. Silicon dioxide and Ni_3S_2 increased the release of alkaline phosphatase, a marker of toxic responses, only slightly. The less acutely toxic compounds caused significant release of alkaline phosphatase. The order of potency in alkaline phosphatase production is OAA > LD = ND > ROFA >> SiO_2 = Ni_3S_2. These results demonstrated that the type of particle used has a strong influence on the biological response.

Dye et al. (1999) carried out reverse transcriptase-polymerase chain reactions on RNA from rat tracheal epithelial cells to evaluate changes in steady-state gene expression of IL-6, MIP-2, and iNOS in cells exposed for 6 h to ROFA (5 μg/cm^2) and Ni, V, or Ni and V(water-soluble equivalent metal solution [pH 3.0]). Expression of MIP-2 and IL-6 genes was significantly upregulated as early as 6 h post-ROFA-exposure in rat tracheal epithelial cells; whereas gene expression of iNOS was maximally increased 24 h postexposure. Vanadium but not Ni appeared to be mediating the effects of ROFA on gene expression. Treatment with dimethylthiourea (4 and 40 mm) inhibited both ROFA and V induced gene expression in a dose-dependent manner.

It appears that many biological responses are produced by PM whether it is composed of a single component or a complex mixture. The newly developed gene array monitors the expressions of many mediator genes that regulate complex and coordinated cellular events involved in tissue injury and repair. Using an array consisting of 27 rat genes representing inflammatory and anti-inflammatory cytokines, growth factors, adhesion molecules, stress proteins, metalloproteinases, vascular tone regulatory molecules, transcription factors, surfactant proteins and antioxidant enzymes, Nadadur et al. (2000) measured pulmonary effects in rats 3 and 24 h following intratracheal instillation of ROFA (3.3 mg/kg), $NiSO_4$ (1.3 μmol/kg), and VSO_4 (2.2 μmol/kg). Their data revealed a two- to three-fold increase in the expression of IL-6 and TIMP-1 at 24 h post-Ni exposure. The expression of cellular fibronectin (cFn-EIIIA) and iNOS increased 24 h following ROFA exposure. Cellular fibronectin, interferon, iNOS, ICAM-1 was increased 24 h following Ni exposure and IL-6 was increased 24 h postexposure in V exposed animals. There was a modest increase in the expression of SP-S and β-actin genes.

There was a 2-fold increase in the expression of IL-6 24 h following exposure to ROFA, Ni, and V using the Northern blot analysis. A densitometric scan of an autoradiograph of blots stripped and reprobed with SP-A cDNA insert indicated a minimal increase in the expression of SP-A, both 3 and 24 h postexposure in all test groups. The findings in this study suggest that gene array may provide a tool for screening the expression profile of tissue specific markers following exposure to PM. However, care should be taken in reviewing such findings because of the variations in dose, instillation versus inhalation, and the time-course for gene expression.

To investigate the interaction between respiratory cells and PM, Kobzik (1995) showed that scavenger receptors are responsible for AM binding of unopsonized PM and that different mechanisms mediate binding of carbonaceous dusts such as DPM. In addition, surfactant components can increase AM phagocytosis of environmental particles in vitro, but only slightly relative to the already avid AM uptake of unopsonized particles (Stringer and Kobzik, 1996). Respiratory tract epithelial cells are also capable of binding with PM to secrete cytokine IL-8. Using a respiratory epithelial cell line (A549), Stringer et al. (1996) found that binding of particles to epithelial cells was calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was not calcium dependent. In addition, as observed in AMs, PM binding by A549 cells also was mediated by scavenger receptors, albeit those distinct from the heparin-insensitive acetylated-LDL receptor. Furthermore, α-quartz, but not TiO_2 or CAPs, caused a dose-dependent production of IL-8 (range 1 to 6 ng/mL), demonstrating a particle-specific spectrum of epithelial cell cytokine (IL-8) response.

7.4.3.3 Other Potential Cellular and Molecular Mechanisms

A potential mechanism involving in the alteration of surface tension may be related to changes in the expression of matrix metalloproteinases (MMPs), such as pulmonary matrilysin and gelatinase A and B, and tissue inhibitor of metalloproteinase (TIMP) (Su et al., 2000a,b). Sprague-Dawley rats exposed to ROFA by intratracheal injection (2.5 mg/rat) had increased mRNA levels of matrilysin, gelatinase A, and TIMP-1. Gelatinase B, not expressed in control animals, was increased significantly from 6 to 24 h following ROFA exposure. Alveolar macrophages, epithelial cells, and inflammatory cells were major cellular sources for the pulmonary MMP expression. The expression of Gelatinase B in rats exposed to the same dose of ambient PM (< 1.7 μm and 1.7 to 3.7 μm) collected from Washington, DC, was significantly increased as compared to saline control; whereas the expression of TIMP-2 was suppressed.

Ambient PM between 3.7 and 20 μm also increased the Gelatinase B expression. Increases in MMPs, which degrade most of the extracellular matrix, suggest that ROFA and ambient PM can similarly increase the total pool of proteolytic activity to the lung and contribute in the pathogenesis of PM-induced lung injury.

The role of sensory nerve receptors in the initiation of PM inflammation has been described in a series of recent studies. Neuropeptide and acid-sensitive sensory irritant (i.e., capsaicin, VR1) receptors were first identified on human bronchial epithelial cells (i.e., BEAS-2B). To address whether PM could initiate airway inflammation through these acid sensitive sensory receptors, BEAS-2B cells were exposed to ROFA and responded with an immediate increase in $[Ca^{+2}]_i$ followed by a concentration-dependent release of inflammatory cytokine (i.e., IL-6, IL-8, TNFα) and their transcripts (Veronesi et al., 1999b). To test the relevance of neuropeptide or capsaicin VR1 receptors to these changes, BEAS-2B cells were pretreated with neuropeptide receptor antagonists or capsazepine (CPZ), the antagonist for the capsaicin (i.e., VR1) receptor. The neuropeptide receptor antagonists reduced ROFA-stimulated cytokine release by 25%-50%. However, pretreatment of cells with CPZ inhibited the immediate increases in $[Ca^{+2}]_i$, diminished transcript (i.e., IL-6, IL-8, TNFα) levels and reduced IL-6 cytokine release to control levels (Veronesi et al., 1999a). The above studies suggested that ROFA inflammation was mediated by acid sensitive VR1 receptors located on the sensory nerve fibers that innervate the airway and on epithelial target cells.

Colloidal particles carry an inherently negative surface charge (i.e., zeta potential) that attracts protons from their vaporous milieu. These protons form a neutralizing, positive ionic cloud around the individual particle (Hunter, 1981). Since VR1 irritant receptors respond to acidity (i.e., protonic charge), experiments were designed to determine if the surface charge carried by ROFA and other PM particles could biologically activate cells and stimulate inflammatory cytokine release. The mobility of ROFA particles was measured in an electrically charged field (i.e., micro-electrophoresis) microscopically and their zeta potential calculated. Next, synthetic polymer microspheres (SPM) (i.e., polymethacrylic acid nitrophenylacrylate microspheres) were prepared with attached carboxyl groups to yield SPM particles with a geometric diameter of 2 ± 0.1 and 6 ± 0.3 μm and with zeta potentials similar to ROFA (−29 + 0.9 mV) particles. These SPM acted as ROFA surrogates with respect to their size and surface charge, but lacked all other contaminants thought to be responsible for its toxicity (e.g., transition metals, sulfates, volatile organics and biologicals). Similar concentrations of SPM and

ROFA particles were used to test BEAS-2B cells and mouse dorsal root ganglia (DRG) sensory neurons, both targets of inhaled PM. Equivalent degrees of biological activation (i.e., increase in intracellular calcium, $[Ca^{+2}]_i$, IL-6 release) occurred in both cell types in response to either ROFA or SPM, and both responses could be reduced by antagonists to VR1 receptors or acid-sensitive pathways. Neutrally charged SPM (i.e., zeta potential of 0 mV), however, failed to stimulate increases in $[Ca^{+2}]_i$ or IL-6 release (Oortgiesen et al., 2000). To expand on these data, a larger set of PM was obtained from urban (St. Louis, Ottawa), residential (wood stove), volcanic (Mt. St. Helen), and industrial (oil fly ash, coal fly ash) sources. Each PM sample was described physicochemically (i.e., size and number of visible particles, acidity, zeta potential) and used to test BEAS-2B epithelial cells. The resulting biological effect (i.e., increases in $[Ca^{+2}]_i$, IL-6 release) was related to their physicochemical descriptions. When examined by linear regression analysis, the only measured physicochemical property that correlated with increases in $[Ca^{+2}]_i$ and IL-6 release was the zeta potential of the visible particles ($r2 > 0.97$) (Veronesi et al., 2002b).

Together, the above studies have demonstrated a neurogenic basis for PM inflammation by which the proton cloud associated with negatively-charged colloidal PM particles can activate acid-sensitive VR1 receptors found on human airway epithelial cells and sensory terminals. This activation results in an immediate influx of calcium and the release of inflammatory neuropeptides and cytokines which proceed to initiate and sustain inflammatory events in the airways through the pathophysiology of neurogenic inflammation (Veronesi and Oortgiesen, 2001).

7.4.4 Specific Particle Size and Surface Area Effects

Most particles used in laboratory animal toxicology studies are greater than 0.1 μm in size. However, the enormous number and huge surface area of ultrafine particles highlight the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm, when inhaled at the same mass concentration, have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5-μm diameter particle; particle surface area is also greatly increased (Table 7-11).

Many studies summarized in 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a), as well as in this document, suggest that the surface of particles or substances that are released from the surface (e.g., transition metals, organics) interact with the biological system,

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 (1996a).

and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean high concentrations of transition metals being available to cause oxidative stress to cells.

Two groups have examined toxicity differences between fine and ultrafine particles, with the general finding that ultrafine particles show a significantly greater response at similar mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). However, only a few studies have investigated the ability of ultrafine particles to generate a greater oxidative stress when compared to fine particles of the same material. Studies by Gilmour et al. (1996) have shown that, at equal mass, ultrafine TiO_2 caused more plasmid DNA strand breaks than fine TiO_2. This effect could be inhibited with mannitol. Osier and Oberdörster (1997) compared the response of rats (F344) exposed by intratracheal inhalation to "fine" (~250 nm) and "ultrafine" (~21 nm) TiO_2 particles with rats exposed to similar doses by intratracheal instillation. Animals receiving particles through inhalation showed a smaller pulmonary response, measured by BAL parameters, in both severity and persistence, when compared with those animals receiving particles through instillation. Ultrafine TiO_2 particles consistently had a significantly greater response than did the fine TiO_2 particles. These results demonstrate a difference in pulmonary response to an inhaled versus an instilled dose, which may result from differences in dose rate, particle distribution, particle surface activity, or altered clearance between the two methods.

Consistent with these in vivo studies, Finkelstein et al. (1997) has shown that exposing primary cultures of rat Type II cells to 10 μg/mL ultrafine TiO_2 (20 nm) causes increased TNF and IL-1 release throughout the entire 48-h incubation period. In contrast, fine TiO_2 (200 nm) had no effect. In addition, ultrafine polystyrene carboxylate-modified microspheres (UFP, fluorospheres, molecular probes 44 ± 5 nm) have been shown to induce a significant enhancement of both substance P and histamine release after administration of capsaicin (10^{-4} M), to stimulate C-fiber, and carbachol (10^{-4} M), a cholinergic agonist in rabbit intratracheally instilled with UFP (Nemmar et al., 1999). A significant increase in histamine release also was recorded in the UFP-instilled group following the administration of both Substance P (10^{-6} M) plus thiorpan (10^{-5} M) and compound 48/80 (C48/80, 10^{-3} M) to stimulate mast cells. Bronchoalveolar lavage analysis showed an influx of PMN, an increase in total protein concentration, and an increase in lung wet weight/dry weight ratio. Electron microscopy showed that both epithelial and endothelial injuries were observed. The pretreatment of rabbits in vivo with a mixture of either SR 140333 and SR 48368, a tachykinin NK_1 and NK_2 receptor antagonist, or a mixture of terfenadine and cimetidine, a histamine H_1 and H_2 receptor antagonist, prevented UFP-induced PMN influx and increased protein and lung WW/DW ratio.

It is believed that ultrafine particles cause greater cellular injury because of the relatively large surface area for a given mass. In addition, the fate of ultrafines after deposition is also different in that they interact more rapidly with epithelial target cells rather than to be phagocytized by alveolar macrophages. However, in a study that compared the response to carbon black particles of two different sizes, Li et al. (1999) demonstrated that in the instillation model, a localized dose of particle over a certain level causes the particle mass to dominate the response, rather than the surface area. Ultrafine carbon black (ufCB, Printex 90), 14 nm in diameter, and fine carbon black (CB, Huber 990), 260 nm in diameter, were instilled intratracheally in rats, and BAL profile at 6 h was assessed. At mass of 125 μg or below, ufCB generated a greater response (increase LDH, epithelial permeability, decrease in GSH, TNF, and NO production) than fine CB at various times postexposure. However, higher doses of CB caused more PMN influx than the ufCB. In contrast to the effect of CB, which showed dose-related increasing inflammatory response, ufCB at the highest dose caused less of a neutrophil influx than at the lower dose, confirming earlier work by Oberdörster et al. (1992). Moreover, when the PMN influx was expressed as a function of surface area, CB produced greater response than ufCB at all doses used in this study. Although particle insterstitialization with a consequent

change in the chemotatic gradient for PMN was offered as an explanation, these results need further scrutiny. Moreover, these findings imply that mass is relatively less important than surface area and that the latter metric may be more useful for assessing PM toxicity. However, it is unclear if this finding is restricted to the particular endpoints addressed and/or carbon black, the PM compound studied.

Oberdörster et al. (2000) recently completed a series of studies in rats and mice using ultrafine particles of various chemical composition. In rats sensitized with endotoxin (70 EU) and exposed to ozone (1 ppm) plus ultrafine carbon particles (~100 $\mu g/m^3$), they found a nine-fold greater release of reactive oxygen species in old rats (20 mo) than in similarly treated young rats (10 wk). Exposure to ultrafine PM alone in sensitized old rats also caused an inflammatory response.

Although the exact mechanism of ultrafine-induced lung injury remains unclear, it is likely that ultrafine particles, because of their small size, are not effectively phagocytized by alveolar macrophages and can easily penetrate the airway epithelium, gaining access to the interstitium. This is particularly significant for ultrafine droplets of acids that do not persist as particles once deposited. However, organic ultrafine particles may persist longer depending on organic components. Using electron microscopy, Churg et al. (1998) examined particle uptake in rat tracheal explants. Explants were submerged in a 5 mg/mL suspension of either fine (0.12 μm) or ultrafine (0.021 μm) TiO_2 particles in Dulbecco's minimal Eagle's medium, without serum and examined after 3 or 7 days. They found both size particles in the epithelium at both time points; but, in the subepithelial tissues, only at day 7. The volume proportion (the volume of TiO_2 over the entire volume of epithelium or subepithelium area) of both fine and ultrafine particles in the epithelium increased from 3 to 7 days. It was greater for ultrafine at 3 days but was greater for fine at 7 days. The volume proportion of particles in the subepithelium at day 7 was equal for both particles, but the ratio of epithelial to subepithelial volume proportion was 2:1 for fine and 1:1 for ultrafine. Ultrafine particles persisted in the tissue as relatively large aggregates; whereas the size of fine particle aggregates became smaller over time. Ultrafine particles appeared to enter the epithelium faster and, once in the epithelium, a greater proportion of them were translocated to the subepithelial space compared to fine particles. However, the authors assumed that the volume proportion is representative of particle number and the number of particles reaching the interstitial space is directly proportional to the number applied (i.e., there is no preferential transport from lumen to interstitium by size). These data are in contrast to the

results of instillation or inhalation of fine and ultrafine TIO_2 particles reported earlier (Ferin et al., 1990, 1992). However, the explant and intratracheal instillation test systems differ in many aspects, making direct comparisons difficult. Limitations of the explant test system include traumatizing the explanted tissue, introducing potential artifacts through the use of liquid suspension for exposure, the absence of inflammatory cells, and possible overloading of the explants with dust.

Only two studies examined the influence of specific surface area on biological activity (Lison et al., 1997; Oettinger et al., 1999). The biological responses to various MnO_2 dusts with different specific surface area (0.16, 0.5, 17, and 62 m^2/g) were compared in vitro and in vivo (Lison et al., 1997). In both systems, the results show that the amplitude of the response is dependent on the total surface area that is in contact with the biological system, indicating that surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles with a specific surface area of 5 m^2/g also were examined in vitro. These particles exhibited an enhanced cytotoxic activity that was almost equivalent to that of particles with a specific surface area of 62 m^2/g, indicating that undefined reactive sites produced at the particle surface by mechanical cleavage also may contribute to the toxicity of insoluble particles. In another study, two types of carbon black particles, Printex 90 (P90, Degussa, Germany, formed by controlled combustion, consists of defined granules with specific surface area of 300 m^2/g and particle size of 14 nm) and FR 101 (Degussa, Germany, with specific surface area of 20 m^2/g and particle size of < 95 nm, has a coarse structure, and the ability to adsorb polycyclic and other carbons) were used in the study (Oettinger et al., 1999). Exposure of AMs to 100 $\mu g/10^6$ cells of FR 101 and P90 resulted in a 1.4- and 2.1-fold increase in ROS release. These exposures also caused a fourfold up-regulation of NF-κB gene expression. These studies indicated that PM of single component with larger surface area produce greater biological response than similar particles with smaller surface area. By exposing bovine AMs to metal oxide coated silica particles, Schluter et al. (1995) showed that most of the metal coatings (As, Ce, Fe, Mn, Ni, Pb, and V) had no effect on ROS production by these cells. However, coating with CuO markedly lowered the O_2^- and H_2O_2, whereas V(IV) increases both reactive oxygen intermediates (ROI). This study demonstrated that, in addition to specific surface area, chemical composition of the particle surface also influences its cellular response.

Thus, ultrafine particles apparently have the potential to significantly contribute to the adverse effects of PM. These studies, however, have overlooked the portion of ambient ultrafine

particles that are not solid in form. Droplets (e.g., sulfuric acid droplets) and organic based ultrafine particles do exist in the ambient environment, but their role in the adverse effects of ultrafine particles has been ignored. Moreover, the ability of these droplet ultrafine particles to spread, disperse, or dissolve after contact with liquid surface layers must be considered. Accordingly, all of the hypotheses and studies should be critically analyzed with regard to the concentrations/doses used, models used, and the specific PM tested.

7.5 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 pathophysiological responses to toxicant exposure is widely acknowledged but poorly understood. Epidemiologic studies have demonstrated that the effects of PM exposure tend to be more evident in populations with pre-existing disease; and it is logical that important mechanistic differences may exist among these populations. However, because of inherent variability (necessitating large numbers of subjects) and ethical concerns associated with using diseased subjects in clinical research studies, a solid database on human susceptibilities is lacking. For more control over both host and environmental variables, animal models often are used. Many laboratory studies have demonstrated alterations in a variety of endpoints in experimental animals following exposure to laboratory-generated particles. These findings (e.g., increased pulmonary inflammation, increased airway resistance, and decrements in pulmonary host defenses) may be of limited value because of uncertainties in extrapolating between the laboratory-generated particles and actual ambient air particle mixes. Thus, care must be taken in extrapolation from animal models of human disease to humans. Rodent models of human disease, their use in toxicology, and the criteria for judging their appropriateness as well as their limitations must be considered (Kodavanti et al., 1998b; Kodavanti and Costa, 1999; Costa, 2000).

7.5.1 Pulmonary Effects of Particulate Matter in Compromised Hosts

Epidemiologic 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. However, an increasing number of newer studies have started to examine effects of ambient particles in compromised host models. For example, Costa and Dreher (1997) used a rat model of cardiopulmonary disease to explore the question of susceptibility and 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). A brief description of the model appears above, in Section 7.3. 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.

Chronic bronchitis is the most prevalent of the COPD-related illnesses. In humans, chronic bronchitis is characterized by pathologic airway inflammation and epithelial damage, mucus cell hyperplasia and hypersecretion, airway obstruction and in advance cases, airway fibrosis. The most widely used animal models of bronchitis (rat and dog) are those produced by subchronic exposure to high concentrations of SO_2 (150 to 600 ppm) for 4 to 6 weeks. Exposure to SO_2

produces changes in the airways similar to those of chronic bronchitis in humans. There is an anatomical difference between the rat and the human in the absence of submucosal glands in the rat. However, like humans, rats exhibit increased airway responsiveness to inhaled bronchoconstricting agonists. Sulfur dioxide-induced lesions include increased numbers of epithelial mucus-producing cell, loss of cilia, airway inflammation, increased pro-inflammatory cytokine expression, and thickening of the airway epithelium. When the cause of the chronic bronchitis is removed, the pathology slowly reverses. The time course and the extent of reversal differs between the human and rodent. Consequently, care should be exercised when applying this model (Kodavanti et al., 1998b).

Respiratory infections are common in all individuals. The infections are generally cleared quickly, depending on the virulence of the organism, however, in individuals with immunologic impairment or lung diseases such a COPD, the residence time in the lung is extended. A variety of viral and bacterial agents have been used to develop infection models in animals. Viral infection models primarily use mice and rats. The models focus on the proliferation and clearance of the microorganisms and the associated pulmonary effect. The models range from highly virulent and lethal (influenza A/Hong Kong/8/68, H3N2) to nonlethal (rat-adapted influenza virus model [RAIV]). The lethal model terminates in extensive pneumonia and lung consolidation. Less virulent models (A/Port Chalmers/1/73 and H3N2) exhibit airway epithelial damage and immune responses. The non-lethal model exhibits airway reactivity that subsides, with recovery being complete in about 2 weeks (Kodavanti et al., 1998b). Bacterial infection models mimic the chronic bacterial infections experienced by humans with other underlying disease conditions. The models develop signs similar to those in humans but to a milder degree. To mimic the more chronic infections, the bacteria are encased in agar beads to prevent rapid clearance. Generally, the models involve pre-exposure to the irritant followed by the bacterial challenge. More recently, bacterial infection models have involved pre-exposure by the bacteria followed by exposure to the irritant (Kodavanti et al., 1998b).

Elder et al. (2000a,b) exposed 8 week to 22 month old Fischer 344 rats and 14- to 17-month-old T_{sk} mice to 100 $\mu g/m^3$ of ultrafine carbon (UF) and/or 1.0 ppm O_3 for six hours following a 12 minute exposure to a low dose (70 EU) of endotoxin (lipopolysaccharide, LPS). The ultrafine carbon had a small effect on lung inflammation and inflammatory cell activation. The effects were enhanced in the compromised lung and in older animals. The greatest effect was in the compromised lung exposed to both ultrafine carbon and ozone.

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; Saldiva et al., 2002). Exposure to concentrated ambient air particles (CAPs) for 5 h/day for 3 days to concentrations ranging from 73.5 to 733 $\mu g/m^3$ 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, 4- and 20-mo-old Fischer 344 rats were examined after exposure to concentrated ambient PM for 5 h/day for 3 consecutive days. They found that exposure to the daily mean concentrations of 80, 170, and 50 $\mu g/m^3$ PM, respectively, produced statistically significant increases in total neutrophil counts (over 10-fold) in lavage fluid of the young, but not the old, rats. Thus, repeated exposure to relatively low concentrations of ambient PM produced an inflammatory response, although the actual percent neutrophils in the concentrated ambient PM-exposed young adult rats was low (approximately 3%). On the other hand, Gordon et al. (2000) found no evidence of neutrophil influx in the lungs of normal and monocrotaline-treated Fischer 344 rats exposed in nine separate experiments to concentrated ambient PM from New York, NY at concentrations as high as 400 $\mu g/m^3$ for a 6-h exposure or 192 $\mu g/m^3$ for three daily 6-h exposures. Similarly, normal and cardiomyopathic hamsters showed no evidence of pulmonary inflammation or injury after a single exposure to the same levels of concentrated ambient PM. Gordon and colleagues did report a statistically significant doubling in protein concentration in lavage fluid in monocrotaline-treated rats exposed for 6 h to 400 $\mu g/m^3$ concentrated ambient PM.

Kodavanti and colleagues (1998b) also have examined the effect of concentrated ambient PM in normal rats and rats with sulfur dioxide-induced chronic bronchitis. Among the four separate exposures to PM, there was a significant increase in lavage fluid protein in bronchitic

rats from only one exposure protocol in which the rats were exposed to 444 and 843 μg/m^3 PM on 2 consecutive days (6 h/day). Neutrophil counts were increased in bronchitic rats exposed to concentrated ambient PM in three of the four exposure protocols, but was decreased in the fourth protocol. No other changes in normal or bronchitic rats were observed, even in the exposure protocols with higher PM concentrations. Thus, rodent studies have demonstrated that inflammatory changes can be produced in normal and compromised animals exposed to concentrated ambient PM. These findings are important because only a limited number of studies have used real-time inhalation exposures to actual ambient urban PM.

Pulmonary function measurements are often less invasive than other means to assess the effects of inhaled air pollutants on the mammalian lung. After publication of the 1996 PM AQCD, a number of investigators examined the response of rodents and dogs to inhaled ambient particles. In general, these investigators have demonstrated that ambient PM has minimal effects on pulmonary function. Gordon et al. (2000) exposed normal and monocrotaline-treated rats to filtered air or 181 μg/m^3 concentrated ambient PM for 3 h. For both normal and monocrotaline-treated rats, no differences in lung volumes or diffusion capacities for carbon monoxide were observed between the air or PM exposed animals at 3 or 24 h after exposure. Similarly, in cardiomyopathic hamsters, concentrated ambient PM had no effect on these same pulmonary function measurements.

Other pulmonary function endpoints have been studied in animals exposed to concentrated ambient PM. Clarke et al. (1999) observed that tidal volume was increased slightly in both control rats and rats with sulfur dioxide-induced chronic bronchitis exposed to 206 to 733 μg/m^3 PM on 3 consecutive days. No changes in peak expiratory flow, respiratory frequency, or minute volume were observed after exposure to concentrated ambient PM. In the series of dog studies by Godleski et al. (2000) (also see Section 7.3), no signficant changes in pulmonary function were observed in normal mongrel dogs exposed to concentrated ambient PM, although a 20% decrease in respiratory frequency was observed in dogs that underwent coronary artery occlusion and were exposed to PM. Thus, studies using normal and compromised animal models exposed to concentrated ambient PM have found minimal biological effects of ambient PM on pulmonary function.

Johnston et al. (1998) exposed 8-week-old mice (young) and 18-mo-old mice (old) to polytetrafluoroethylene (PTFE) fumes (0, 10, 25, and 50 μg/m^3) for 30 min. Lung lavage endpoints (PMN, protein, LDH, and β-glucuronidase) as well as lung tissue mRNA levels for

various cytokines, metallothionein and for Mn superoxide dismutase were measured 6 h following exposure. Protein, lymphocyte, PMN, and TNF-α mRNA levels were increased in older mice when compared to younger mice. These findings suggest that the inflammatory response to PTFE fumes is altered with age, being greater in the older animals. Although ultrafine PTFE fumes are not a valid surrogate for ambient ultrafine particles (Oberdörster et al., 1992), this study provides evidence supporting the hypothesis that particle-induced pulmonary inflammation differs between young and old mice. Other studies on age-related PM effects are described in Section 7.6 (Responses to PM and Gaseous Pollutant Mixtures).

Kodavanti et al. (2000b; 2001) used genetically predisposed spontaneously hypertensive (SH) rats as a model of cardiovascular disease to study PM-related susceptibility. The SH rats were found to be more susceptible to acute pulmonary injury from intratracheal ROFA exposure than normotensive control Wistar Kyoto (WKY) rats (Kodavanti et al., 2001). The primary metal constituents of ROFA, V and Ni, caused differential species-specific effects. Vanadium, which was less toxic than Ni in both strains, caused inflammatory responses only in WKY rats; whereas Ni was injurious to both WKY and SH rats (SH > WKY). This differential responsiveness of V and Ni was correlated with their specificity for airway and parenchymal injury, discussed in another study (Kodavanti et al., 1998b). When exposed to the same ROFA by inhalation (15 mg/m^3, 6 h/d, 3 days), SH rats were more sensitive than WKY rats in regards to vascular leakage (Kodavanti et al., 2000b). The SH rats exhibited a hemorrhagic response to ROFA. Oxidative stress was much higher in ROFA exposed SH rats than matching WKY rats. Also, SH rats, unlike WKY rats, showed a compromised ability to increase BALF glutathione in response to ROFA, suggesting a potential link to increased susceptibility. However, lactate dehydrogenase and n-acetylglucosaminidase activities were higher in WKY rats. Lactate dehydrogenase was slightly higher in SH rats instilled with ROFA (Kodavanti et al., 2001). Cardiovascular effects were characterized by ST-segment area depression of the ECG in ROFA-exposed SH but not WKY rats. When the same rats were exposed to ROFA by inhalation to 15 mg/m^3, 6 h/d, 3 d/wk for 1, 2, or 4 wk compared to intratracheal exposure to 0, 1.0, 5.0 mg/kg in saline (Kodavanti et al., 2002), differences in effects were dependent on the length of exposure. After acute exposure, increased plasma fibrinogen was associated with lung injury; longer-term, episodic ROFA exposure resulted in progressive protein leakage and inflammation that was significantly worse in SH rats when compared to WKY rats. These studies demonstrate the potential utility of cardiovascular disease models for the study of PM health effects and show

that genetic predisposition to oxidative stress and cardiovascular disease may play a role in increased sensitivity to PM-related cardiopulmonary injury.

On the basis of in vitro studies, Sun et al. (2001) predicted that the antioxidant and lipid levels in the lung lining fluid may determine susceptibility to inhaled PM. In a subsequent study from the same laboratory, Norwood et al. (2001) conducted inhalation studies on guinea pigs to test this hypothesis. On the basis of dietary supplementation or depletion of ascorbic acid (C) and glutathione (GSH) the guinea pigs were divided into four groups: (+C + GSH), (+C – GSH), (–C + GSH), and (–C – GSH). All groups were exposed (nose-only) to clean air or 19-25 mg/m^3 ROFA (< 2.5 μm) for 2 h. Nasal lavage and BAL fluid and cells were examined at 0 h and 24 h postexposure. Exposure to ROFA increased lung injury in the (-C-GSH) group only (as shown by increased BAL fluid protein, LDH, and PMNs and decreased BAL macrophages) and resulted in lower antioxidant concentrations in BAL fluid than were found with single deficiencies.

In summary, although more of these studies are just beginning to emerge and are only now being replicated or followed more thoroughly to investigate underlying mechanisms, they do provide evidence suggestive of enhanced susceptibility to inhaled PM in "compromised" hosts.

7.5.2 Genetic Susceptibility to Inhaled Particles and their Constituents

A key issue in understanding adverse health effects of inhaled ambient PM is identification of which classes of individuals are susceptible to PM. Although factors such as age and health status have been studied in both epidemiology and toxicology studies, some investigators have begun to examine the importance of genetic susceptibility in the response to inhaled particles because of evidence that genetic factors play a role in the response to inhaled pollutant gases. To accomplish this goal, investigators typically have studied the interstrain response to particles in rodents. The response to ROFA instillation in different strains of rats has been investigated by Kodavanti et al. (1996, 1997a). In the first study, male Sprague-Dawley (SD) and Fischer-344 (F-344) rats were instilled intratracheally with saline or ROFA particles (8.3 mg/kg). ROFA instillation produced an increase in lavage fluid neutrophils in both SD and F-344 rats; whereas a time-dependent increase in eosinophils occurred only in SD rats. In the subsequent study (Kodavanti et al., 1997a), SD, Wistar (WIS), and F-344 rats (60 days old) were exposed to saline or ROFA (8.3 mg/kg) by intratracheal instillation and examined for up to 12 weeks. Histology indicated focal areas of lung damage showing inflammatory cell infiltration as well as alveolar,

airway, and interstitial thickening in all three rat strains during the week following exposure. Trichrome staining for fibrotic changes indicated a sporadic incidence of focal alveolar fibrosis at 1, 3, and 12 weeks in SD rats; whereas WIS and F-344 rats showed only a modest increase in trichrome staining in the septal areas. One of the isoforms of fibronectin mRNA was upregulated in ROFA-exposed SD and WIS rats, but not in F-344 rats. Thus, in rats there appears to be a genetic based difference in susceptibility to lung injury induced by instilled ROFA.

Differences in the degree of pulmonary inflammation have been described in rodent strains exposed to airborne pollutants. To understand the underlying causes, signs of airway inflammation (i.e., airway hyper-responsiveness, inflammatory cell influx) were established in responsive (BABL/c) and non-responsive (C57BL/6) mouse strains exposed to ROFA (Veronesi et al., 2000). Neurons taken from the ganglia (i.e., dorsal root ganglia) that innervate the nasal and upper airways were cultured from each mouse strain and exposed to 25 or 50 μg/mL ROFA for 4 h. The difference in inflammatory response noted in these mouse strains in vivo was retained in culture, with C57BL/6 neurons showing significantly lower signs of biological activation (i.e., increased intracellular calcium levels) and cytokine (i.e., IL-6, IL-8) release relative to BALB/c mice. RT-PCR and immunocytochemistry indicated that the BALB/c mouse strain had a significantly higher number of neuropeptide and acid-sensitive (i.e., NK1, VR1) sensory receptors on their sensory ganglia relative to the C57BL/6 mice. Such data indicate that genetically-determined differences in sensory inflammatory receptors can influence the degree of PM-induced airway inflammation.

Kleeberger and colleagues have examined the role that genetic susceptibility plays in the effect of inhaled acid-coated particles on macrophage function. Nine inbred strains of mice were exposed nose-only to carbon particles coated with acid (10 mg/m^3 carbon with 285 μg/m^3 sulfate) for 4 h (Ohtsuka et al., 2000a). Significant inter-strain differences in Fc-receptor-mediated macrophage phagocytosis were seen with C57BL/6J mice being the most sensitive. Although neutrophil counts were increased more in C3H/HeOuJ and C3H/HeJ strains of mice than in the other strains, the overall magnitude of change was small and not correlated with the changes in macrophage phagocytosis. In follow-up studies using the same type particle, Ohtsuka et al. (2000a,b) performed a genome-wide scan with an intercross cohort derived from C57BL/6J and C3H/HeJ mice. Analyses of phenotypes of segregant and nonsegregant populations derived from these two strains indicate that two unlinked genes control susceptibility. They identified a

3-centiMorgan segment on mouse chromosome 17 that contains an acid-coated particle susceptibility locus. Interestingly, this quantitative trait locus (a) overlaps with those described for ozone-induced inflammation (Kleeberger et al., 1997) and acute lung injury (Prows et al., 1997) and (b) contains several promising candidate genes that may be responsible for the observed genetic susceptibility for macrophage dysfunction in mice exposed to acid-coated particles.

Leikauf and colleagues (Leikauf et al., 2000; Wesselkamper et al., 2000; McDowell et al., 2000; Prows and Leikauf, 2001; Leikauf et al., 2001) have identified a genetic susceptibility in mice that is associated with mortality following exposures to high concentrations (from 15 to 150 $\mu g/m^3$) of a NiSO4 aerosol (0.22 μm MMAD) for up to 96 h. These studies also have preliminarily identified the chromosomal locations of a few genes that may be responsible for this genetic susceptibility. This finding is particularly significant in light of the toxicology studies demonstrating that bioavailable, first-row transition metals participate in acute lung injury following exposure to emission and ambient air particles. Similar genes may be involved in human responses to particle-associated metals; but additional studies are needed to determine whether the identified metal susceptibility genes are involved in human responses to ambient levels of particulate-associated metals.

One study has examined the interstrain susceptibility to ambient particles. C57BL/6J and C3H/HeJ mice were exposed to 250 $\mu g/m^3$ concentrated ambient $PM_{2.5}$ for 6 h and examined at 0 and 24 h after exposure for changes in lavage fluid parameters and cytokine mRNA expression in lung tissue (Shukla et al., 2000). No interstrain differences in response were observed. Surprisingly, although no indices of pulmonary inflammation or injury were increased over control values in the lavage fluid, increases in cytokine mRNA expression were observed in both murine strains exposed to $PM_{2.5}$. Although the increase in cytokine mRNA expression was generally small (approximately twofold), the effects on IL-6, TNF-α, TGF-β2, and γ-interferon were consistent.

Thus, a handful of studies have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled particles. However, the doses of PM administered in these studies, whether by inhalation or instillation, were extremely high when compared to ambient PM levels. Similar strain differences in response to inhaled metal particles have been observed by other investigators (McKenna et al., 1998; Wesselkamper et al., 2000), although the concentration of metals used in these studies were also more relevant to occupational rather than

environmental exposure levels. The extent to which genetic susceptibility plays as significant a role in the adverse effects of ambient PM as does age or health status remains to be determined.

7.5.3 Particulate Matter Effects on Allergic Hosts

Relatively little is known about the effects of inhaled particles on humoral (antibody) or cell-mediated immunity. Alterations in the response to a specific antigenic challenge have been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 $\mu g/m^3$) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to nonspecific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This nonspecific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although, its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized to either specific or nonspecific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Jacobs et al., 1997; Lipsett et al., 1997). Combustion particles also may serve as carrier particles for allergens (Knox et al., 1997).

A number of in vivo and in vitro studies have demonstrated that diesel particles (DPM) can alter the immune response to challenge with specific antigens and suggest that DPM may act as an adjuvant. These studies have shown that treatment with DPM enhances the secretion of antigen-specific IgE in mice (Takano et al., 1997) and in the nasal cavity of human subjects (Diaz-Sanchez et al., 1996, 1997; Ohtoshi et al., 1998; Nel et al., 2001). Because IgE levels play a major role in allergic asthma (Wheatley and Platts-Mills, 1996), upregulation of its production could lead to an increased response to inhaled antigen in particle-exposed individuals.

Van Zijverden et al. (2000) and Van Zijverdan and Granum (2000) used mouse models to assess the potency of particles (diesel, carbon black, silica) to adjuvate an immune response to a protein antigen. All particles exert an adjuvant effect on the immune response to co-administered antigen, apparently stimulated by the particle core rather than the attached chemical factors. Different particles, however, stimulate distinct types of immune responses. In one model (Van Zijverden et al., 2001), BALB/c mice were intranasally treated with a mixture of antigen (model antigen TNP-Ovalbumin, TNP-OVA) and particles on three consecutive days. On day 10 after sensitization, mice were challenged with the antigen TNP-OVA alone, and five

days later the immune response was assessed. Diesel particulate matter, as well as carbon black particles (CB), were capable of adjuvating the immune response to TNP-OVA as evidenced by an increase of TNP-specific antibody (IgG1 and IgE) secreting B cells antibodies in the lung-draining lymph nodes. Increased antigen-specific IgG1, IgG2a, and IgE isotypes were measured in the serum, indicating that the response resulted in systemic sensitization. Importantly, an increase of eosinophils in the bronchio-alveolar lavage was observed with CB. Companion studies with the intranasal exposure model showed that the adjuvant effect of CB particles was even more pronounced when the particles were given during both the sensitization and challenge phases; whereas administration during the challenge phase caused only marginal changes in the immune response. These data show that PM can increase both the sensitization and challenge responses to a protein antigen, and the immune stimulating activity of particles appears to be a time-dependent process, suggesting that an inflammatory microenvironment (such as may be created by the particles) is crucial for enhancing sensitization by particles.

Only a small number of studies have examined mechanisms underlying the enhancement of allergic asthma by ambient urban particles. Ohtoshi et al. (1998) reported that a coarse size-fraction of resuspended ambient PM, collected in Tokyo, induced the production of granulocyte macrophage colony stimulating factor (GMCSF), an upregulator of dendritic cell maturation and lymphocyte function, in human airway epithelial cells in vitro. In addition to increased GMCSF, epithelial cell supernatants contained increased IL-8 levels when incubated with DPM, a principal component of ambient particles collected in Tokyo. Although the sizes of the two types of particles used in this study were not comparable, the results suggest that ambient PM, or at least the DPM component of ambient PM, may be able to upregulate the immune response to inhaled antigen through GMCSF production. Similarly, Takano et al. (1998) has reported airway inflammation, airway hyperresponsiveness, and increased GMGSF and IL-5 in mice exposed to diesel exhaust.

In a study by Walters et al. (2001), PM_{10} was found to induce airway hyperresponsiveness, suggesting that PM exposure may be an important factor in increases in asthma prevalence. Naive mice were exposed to a single dose (0.5 mg/ mouse) of ambient PM, coal fly ash, or diesel PM. Exposure to PM_{10} induced increases in airway responsiveness and BAL cellularity; whereas diesel PM induced significant increases in BAL cellularity, but not airway responsiveness. On the other hand, coal fly ash exposure did not elicit significant changes in either of these parameters. Ambient PM-induced airway hyperresponsiveness was sustained over 7 days. The

increase in airway responsiveness was preceded by increases in BAL eosinophils; whereas a decline in airway responsiveness was associated with increases in macrophages. Thus, ambient PM can induce asthma-like parameters in naive mice.

Several other studies have examined in greater detail the contribution of the particle component and the organic fraction of DPM to allergic asthma. Tsien et al. (1997) treated transformed IgE-producing human B lymphocytes in vitro with the organic extract of DPM. The organic phase extraction had no effect on cytokine production but did increase IgE production. In these in vitro experiments, DPM appeared to be acting on cells already committed to IgE production, thus suggesting a mechanism by which the organic fraction of combustion particles can directly affect B cells and influence human allergic asthma.

Cultured epithelial cells from atopic asthmatics show a greater response to DPM exposure when compared with cells from nonatopic nonasthmatics. IL-8, GM-CSF, and soluble ICAM-1 increased in response to DPM at a concentration of 10 μg/mL DPM (Bayram et al., 1998a,b). This study suggests that particles could modulate airway disease through their actions on airway epithelial cells. This study also suggests that bronchial epithelial cells from asthmatics are different from those of nonasthmatics in regard to their mediator release in response to DPM.

Sagai and colleagues (1996) repeatedly instilled mice with DPM for up to 16 weeks and found increased numbers of eosinophils, goblet cell hyperplasia, and nonspecific airway hyperresponsiveness, changes which are central features of chronic asthma (National Institutes of Health, 1997). Takano et al. (1997) extended this line of research and examined the effect of repeated instillation of DPM on the antibody response to antigen OVA in mice. They observed that antigen-specific IgE and IgG levels were significantly greater in mice repeatedly instilled with both DPM and OVA. Because this upregulation in antigen-specific immunoglobulin production was not accompanied by an increase in inflammatory cells or cytokines in lavage fluid, it would suggest that, in vivo, DPM may act directly on immune system cells, as described in the work by Tsien et al. (1997). Animal studies have confirmed that the adjuvant activity of DPM also applies to the sensitization of Brown-Norway rats to timothy grass pollen (Steerenberg et al., 1999).

Diaz-Sanchez and colleagues (1996) have continued to study the mechanism of DPM-induced upregulation of allergic response in the nasal cavity of human subjects. In one study, a 200 μL aerosol bolus containing 0.15 mg of DPM was delivered into each nostril of subjects with or without seasonal allergies. In addition to increases in IgE in nasal lavage fluid (NAL),

they found an enhanced production of IL-4, IL-6, and IL-13, cytokines known to be B cell proliferation factors. The levels of several other cytokines also were increased, suggesting a general inflammatory response to a nasal challenge with DPM. In a following study, these investigators delivered ragweed antigen, alone or in combination with DPM, on two occasions, to human subjects with both allergic rhinitis and positive skin tests to ragweed (Diaz-Sanchez et al., 1997). They found that the combined challenge with ragweed antigen and DPM produced significantly greater antigen-specific IgE and IgG4 in NAL. A peak response was seen at 96 h postexposure. The combined treatment also induced expression of IL-4, IL-5, IL-10, and IL-13, with a concomitant decrease in expression of Th1-type cytokines. Although the treatments were not randomized (antigen alone was given first to each subject), the investigators reported that pilot work showed no interactive effect of repeated antigen challenge on cellular and biochemical markers in NAL. Diesel particulate matter also resulted in the nasal influx of eosinophils, granulocytes, monocytes, and lymphocytes, as well as the production of various inflammatory mediators. The combined DPM plus ragweed exposure did not increase the rhinitis symptoms beyond those of ragweed alone. Thus, diesel exhaust (particles and gases) can produce an enhanced response to antigenic material in the nasal cavity.

Extrapolation of these findings of enhanced allergic response in the nose to the human lung would suggest that ambient combustion particles containing DPM may have significant effects on allergic asthma. A study by Nordenhall et al. (2001) has addressed the effects of diesel PM on airway hyperresponsiveness, lung function and airway inflammation in a group of atopic asthmatics with stable disease. All were hyperresponsive to methacholine. Each subject was exposed to DPM (300 $\mu g/m^3$) and air for 1 h on two separate occasions. Lung function was measured before and immediately after the exposures. Sputum induction was performed 6 h, and methacholine inhalation test 24 h, after each exposure. Exposure to DE was associated with a significant increase in the degree of hyperresponsiveness, as compared to after air, a significant increase in airway resistance and in sputum levels of interleukin (IL)-6 ($p=0.048$). No changes were detected in sputum levels of methyl-histamine, eosinophil cationic protein, myeloperoxidase, and IL-8.

These studies provide biological plausibility support for the exacerbation of allergic asthma likely being associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities and countries that rely

heavily on diesel-powered vehicles; and number concentrations of ultrafine DPM may be increasing due to manufacture and use of modern diesel engines, in contrast to decreases in DPM mass concentrations over the past decades.

In an examination of the effect of concentrated ambient PM on airway responsiveness in mice, Goldsmith et al. (1999) exposed control and ovalbumin-sensitized mice to an average concentration of 787 $\mu g/m^3$ PM for 6 h/day for 3 days. Although ovalbumin sensitization itself produced an increase in the nonspecific airway responsiveness to inhaled methylcholine, concentrated ambient PM did not change the response to methylcholine in ovalbumin-sensitized or control mice. For comparison, these investigators examined the effect of inhalation of an aerosol of the active soluble fraction of ROFA on control and ovalbumin-sensitized mice and found that ROFA could produce nonspecific airway hyperresponsiveness to methylcholine in both control and ovalbumin-sensitized mice. Similar increases in airway responsiveness have been observed after exposure to ROFA in normal and ovalbumin-sensitized rodents (Gavett et al., 1997, 1999; Hamada et al., 1999, 2000).

Gavett et al. (1999) have investigated the effects of ROFA (intratracheal instillation) in ovalbumin (OVA) sensitized and challenged mice. Instillation of 3 mg/kg (approximately 60 µg) ROFA induced inflammatory and physiological responses in the OVA mice that were related to increases in Th2 cytokines (IL-4, IL-5). Compared to OVA sensitization alone, ROFA induced greater than additive increases in eosinophil numbers and in airway responsiveness to methylcholine.

Hamada et al. (1999, 2000) have examined the effect of a ROFA leachate aerosol in a neonatal mouse model of allergic asthma. In the first study, neonatal mice sensitized by intraperitoneal (ip) injection with OVA developed airway hyperresponsiveness, eosinophilia, and elevated serum anti-ovalbumin IgE after a challenge with inhaled OVA. Exposure to the ROFA leachate aerosol had no marked effect on the airway responsiveness to inhaled methacholine in nonsensitized mice, but did enhance the airway hyperresponsiveness to methylcholine produced in OVA-sensitized mice. No other interactive effects of ROFA exposure with OVA were observed. In a subsequent study, Hamada et al. clearly demonstrated that, whereas inhaled OVA alone was not sufficient to sensitize mice to a subsequent inhaled OVA challenge, pretreatment with a ROFA leachate aerosol prior to the initial exposure to aerosolized OVA resulted in an allergic response to the inhaled OVA challenge. Thus, exposure to a ROFA leachate aerosol can

alter the immune response to inhaled OVA both at the sensitization stage at an early age and at the challenge stage.

Lambert et al. (1999) and Gilmour et al. (2001) also examined the effect of ROFA on a rodent model of pulmonary allergy. Rats were instilled intratracheally with 200 or 1,000 μg ROFA 3 days prior to sensitization with house dust mite (HDM) antigen. HDM sensitization after 1,000 μg ROFA produced increased eosinophils, LDH, BAL protein, and IL-10 relative to HDM alone. Although ROFA treatment did not affect antibody levels, it did enhance pulmonary eosinophil numbers. The immediate bronchoconstrictive and associated antigen-specific IgE response to a subsequent antigen challenge was increased in the ROFA-treated group in comparison with the control group. Together, these studies suggest the components of ROFA can augment the immune response to antigen.

Evidence that metals are responsible for the ROFA-enhancement of an allergic sensitization was demonstrated by Lambert et al. (2000). In this follow-up study, Brown Norway rats were instilled with 1 mg ROFA or the three main metal components of ROFA (iron, vanadium, or nickel) prior to sensitization with instilled house dust mite. The three individual metals were found to augment different aspects of the immune response to house dust mite. Nickel and vanadium produced an enhanced immune response to the antigen as seen by higher house dust mite-specific IgE serum levels after an antigen challenge at 14 days after sensitization. Nickel and vanadium also produced an increase in the lymphocyte proliferative response to antigen in vitro. In addition, the antigen-induced bronchoconstrictive response was greater only in nickel-treated rats. Thus, instillation of metals at concentrations equivalent to those present in the ROFA leachate mimicked the response to ROFA, suggesting that the metal components of ROFA are responsible for the increased allergic sensitization observed in ROFA-treated animals.

Although these studies demonstrate that inhalation or instillation of ROFA augments the immune response in allergic hosts, the applicability of these findings to ambient PM is an important consideration. Goldsmith et al. (1999) have compared the effect of inhalation of concentrated ambient PM for 6 h/day for 3 days versus the effect of a single exposure to a ROFA leachate aerosol on the airway responsiveness to methylcholine in OVA-sensitized mice. Exposure to ROFA leachate aerosols significantly enhanced the airway hyperresponsiveness in OVA-sensitized mice; whereas exposure to concentrated ambient PM (average concentration of 787 $\mu g/m^3$) had no effect on airway responsiveness in six separate experiments. Thus, the effect

of the ROFA leachate aerosols on the induction of airway hyperresponsiveness in allergic mice was significantly different than that of a high concentration of concentrated ambient PM. Although airway responsiveness was examined at only one post-exposure time point, these findings do suggest that a great deal of caution should be used in interpreting the results of studies using ROFA particles or leachates in the attempt to investigate the biologic plausibility of the adverse health effects of PM.

7.5.4 Resistance to Infectious Disease

The development of an infectious disease requires both the presence of the appropriate pathogen, as well as host susceptibility to the pathogen. There are numerous specific and nonspecific host defenses against microbes, and the ability of inhaled particles to modify resistance to bacterial infection could result from a decreased ability to clear or kill microbes. Rodent infectivity models frequently have been used to examine the effect of inhaled particles on host defense and infectivity. Mice or rats are challenged with a bacterial or viral load either before or after exposure to the particles (or gas) of interest; mortality rate, survival time, or bacterial clearance are then examined. A number of studies that have used the infectivity model to assess the effect of inhaled PM were discussed previously (U.S. Environmental Protection Agency, 1982, 1989, 1996a). In general, acute exposure to sulfuric acid aerosols at concentrations up to 5,000 $\mu g/m^3$ were not very effective in enhancing mortality in a bacterially mediated murine model. In rabbits, however, sulfuric acid aerosols altered anti-microbial defenses after exposure for 2 h/day for 4 days to 750 $\mu g/m^3$ (Zelikoff et al., 1994). Acute or short-term repeated exposures to high concentrations of relatively inert particles have produced conflicting results. Carbon black (10,000 $\mu g/m^3$) was found to have no effect on susceptibility to bacterial infection (Jakab, 1993); whereas TiO_2 (20,000 $\mu g/m^3$) decreased the clearance of microbes and the bacterial response of lymphocytes isolated from mediastinal lymph nodes (Gilmour et al., 1989a,b). In addition, exposure to DPM (2 mg/m^3, 7h/d, 5d/wk for 3 and 6 mo) has been shown to enhance the susceptibility of mice to the lethal effects of some, but not all, microbial agents (Hahon et al., 1985). Thus, the pulmonary response to microbial agents has been shown to be altered at relatively high particle concentrations in animal models. Moreover, these effects appear to be highly dependent on the microbial challenge and the test animal studied. Pritchard et al. (1996) observed in rats exposed to particles with a high concentration of

metals (e.g., ROFA), that the increased mortality rate after streptococcus infection was associated with the amount of metal in the PM.

There are few recent studies that have examined mechanisms potentially responsible for the effect of PM on infectivity. In one study, Cohen and colleagues (1997) examined the effect of inhaled vanadium (V) on immunocompetence. Healthy rats were repeatedly exposed to 2 mg/m^3 V, as ammonium metavanadate, and then instilled with polyinosinic-polycytidilic acid (poly I:C), a double-stranded polyribonucleotide that acts as a potent immunomodulator. Induction of increases in lavage fluid protein and neutrophils was greater in animals preexposed to V. Similarly, IL-6 and interferon-gamma were increased in V-exposed animals. Alveolar macrophage function, as determined by zymosan-stimulated superoxide anion production and by phagocytosis of latex particles, was depressed to a greater degree after poly I:C instillation in V-exposed rats as compared to filtered air-exposed rats. These findings provide evidence that inhaled V, a trace metal found in combustion particles and shown to be toxic in vivo in studies using instilled or inhaled ROFA (Dreher et al., 1997; Kodavanti et al., 1997b, 1999), has the potential to inhibit the pulmonary response to microbial agents. However, it must be remembered that these effects were found at very high exposure concentrations of V, and as with many studies, care must be taken in extrapolating the results to the ambient exposure of healthy individuals or those with preexisting cardiopulmonary disease to trace concentrations (~3 orders of magnitude lower concentration) of metals in ambient PM.

7.6 RESPONSES TO PARTICULATE MATTER AND GASEOUS POLLUTANT MIXTURES

Ambient PM itself is a mixture of particles of varying size and composition. The following discussion examines effects of mixtures of ambient PM, or PM surrogates, with gaseous pollutants. Ambient PM co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide and innumerable other non-PM components that are not routinely measured. Toxicological interactions between PM and gaseous co-pollutants may be antagonistic, additive, or synergistic (Mauderly, 1993). The presence and nature of any interaction appears to depend on the chemical composition, size, concentration and ratios of pollutants in the mixture, exposure duration, and the endpoint being examined. It may be difficult to predict *a priori* from the presence of certain

pollutants whether any interaction will occur and, if there is interaction, whether it will be synergistic, additive, or antagonistic (Table 7-12).

Mechanisms responsible for the various forms of interaction are speculative. In terms of potential health effects, the greatest hazard from pollutant interaction is the possibility of synergy between particles and gases, especially if effects occur at concentrations at which no effects occur when individual constituents are inhaled. Various physical and chemical mechanisms may underlie synergism. For example, physical adsorption or absorption of some material on a particle could result in transport to more sensitive sites, or sites where this material would not normally be deposited in toxic amounts. This physical process may explain the interaction found in studies of mixtures of carbon black and formaldehyde or of carbon black and acrolein (Jakab, 1992, 1993).

Chemical interactions between PM and gases can occur on particle surfaces, thus forming secondary products whose surface layers may be more active toxicologically than the primary materials and that can then be carried to a sensitive site. The hypothesis of such chemical interactions has been examined in the gas and particle exposure studies by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992) and Jakab and colleagues (Jakab and Hemenway, 1993; Jakab et al., 1996). These investigators have suggested that synergism occurs as secondary chemical species are produced, especially under conditions of increased temperature and relative humidity.

Another potential mechanism of gas-particle interaction may involve a pollutant-induced change in the local microenvironment of the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) suggested that the observed synergism between ozone (O_3) and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of O_3 by producing a change in the reactivity or residence time of reactants, such as radicals, involved in O_3-induced tissue injury. Likewise, Pinkerton et al. (1989) showed increased retention of the mass and number of asbestos fibers in rats exposed to O_3, suggesting an increase in lung fiber burden due to exposure to this gaseous pollutant.

Vincent et al. (1997) exposed rats to 0.8 ppm O_3 in combination with 5 or 50 mg/m^3 of resuspended urban particles for 4 h. Although PM alone caused no change in cell proliferation (^{3}H-thymidine 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

TABLE 7-12. RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT 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/m^3 carbon + 70 µg/m^3 ammonium bisulfate + 0.2 ppm O_3 or 100 µg/m^3 carbon +140 µg/m^3 ammonium bisulfate + 0.2 ppm O_3	0.4 µm MMAD $\sigma g = 2.0$	4 h/day, 3 days/week for 4 weeks	No changes in protein concentration in lavage fluid or in prolyl 4-hydroxylase activity in blood. Slight, but statistically significant decreases in plasma fibronectin in animals exposed to the combined atmospheres compared to animals exposed to O_3 alone.	Bolarin et al. (1997)
Rats	O_3 and Ottawa urban dust	Inhalation	40,000 µg/m^3 and 0.8 ppm O_3	4.5 µm MMAD	Single 4-h exposure followed by 20 h clean air	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/m^3 120 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 children 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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-12 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT 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
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)
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 µg/m^3 carbon with or without 5 to 20 ppm SO_2 at 10% or 85% RH	0.3 µm MMAD σg = 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) Clark et al. (2000)
Rats, S-D, male, 250-300 g	H_2SO_4 and O_3	Inhalation, nose-only	500 µg/m^3 H_2SO_4 aerosol (two different particle sizes), with or without 0.6 ppm O_3	Fine (0.3 µm MMD, σg = 1.7) and ultrafine (0.06 µm, σg = 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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-12 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT 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, S-D 300 g	O_3 and H_2SO_4-coated carbon	Inhalation, nose-only	0.2 ppm O_3 + 50 µg/m^3 C + 100 µg/m^3 H_2SO_4 0.4 ppm O_3 +250 µg/m^3 C +500 µg/m^3 H_2SO_4	0.26 µm σg = 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 µm/m^3 ammonium Bisulfate 70 µg/m^3	0.46 µm 0.3 µm	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 µg/m^3 0.3 ppm	$PM_{2.5}$	5 h	A small increase in pulmonary resistance and airway responsiveness was found in both normal mice and mice with ovalbumin-induced asthma immediately after exposure to CAPs, but not O_3; no evidence of synergy; activity attributed to the AlSi PM component.	Kobzik et al. (2001)
Rats	H_2SO_4 and O_3	Inhalation, whole body	20 to 150 µg/m^3 H_2SO_4 and 0.12 or 0.2 ppm O_3	0.4 to 0.8 µm	Intermittent (12 h/day) or continuous exposure for up to 90 days	No interactive effect of H_2SO_4 and O_3 on biochemical and morphometric endpoints.	Last and Pinkerton (1997)
Humans, children, healthy and asthmatic	H_2SO_4, SO_2, and O_3	Inhalation	60 to 140 µg/m^3 H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3	0.6 µm H_2SO_4	Single 4-h exposure with intermittent exercise	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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 7-12 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT 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, 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 µg/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)

DRAFT-DO NOT QUOTE OR CITE

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 (0.6 ppm) and fine (MMD = 0.3 μm) or ultrafine (MMD = 0.06 μm) H_2SO_4 aerosols (0.5 mg/m^3) on rat lung morphology. They determined morphometrically that alveolar septal volume was increased in animals 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 μg/m^3 H_2SO_4) had no interactive effect on the biochemical and morphometric changes produced by either intermittent or continuous O_3 exposure (0.12 to 0.2 ppm). Thus, the interactive effects of O_3 and acid aerosol co-exposure in the lung disappeared during the long-term exposure.

Kleinman et al. (1999) examined the effects of O_3 (0.2 and 0.4 ppm) plus fine (MMAD = 0.26 μm), H_2SO_4-coated, carbon particles (100, 250, and 500 μg/m^3) for 1 or 5 days. They found the inflammatory response with the O_3-particle mixture was greater after 5 days (4 h/day) than after Day 1. This contrasted with O_3 exposure alone (0.4 ppm), which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure.

Kleinman et al. (2000) examined the effects of a mixture of elemental carbon particles (50 μg/m^3), O_3 (0.2 ppm), and ammonium bisulfate (70 μg/m^3) on rat lung collagen content and macrophage activity. 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 et al. (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.

Studies have examined interactions between carbon particles and gaseous co-pollutants. Jakab et al. (1996) and Clarke et al. (2000c) challenged mice with a single 4-h exposure to a high concentration of carbon particles (10 mg/m^3) in the presence of 10 ppm SO_2 (~140 μg $cpSO_4^{2-}$) at low and high relative humidities. Macrophage phagocytosis was depressed significantly only in

mice exposed to the combined pollutants under high relative humidity (85%) conditions. There was no evidence of an inflammatory response based on total cell counts and differential cell counts from BAL; however, macrophage phagocytosis remained depressed for 7 to 14 days. Intrapulmonary bactericidal activity also was suppressed and remained suppressed for 7 days. This study suggests that fine carbon particles can serve as an effective carrier for acidic sulfates where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days postexposure. Bolarin et al. (1997) exposed rats to only 50 or 100 $\mu g/m^3$ carbon particles in combination with ammonium bisulfate and O_3. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus O_3 alone. Thus as, previously noted, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors, including the gaseous co-pollutant, concentration, and time.

In a complex series of exposures, Oberdörster and colleagues examined the interaction of ultrafine carbon particles (100 $\mu g/m^3$) and O_3 (1 ppm) in young and old Fischer 344 rats that were pretreated with aerosolized endotoxin (Elder et al., 2000a,b). In old rats, exposure to carbon and O_3 produced an interaction that resulted in a greater influx in neutrophils than that produced by either agent alone. This interaction was not seen in young rats. Oxidant release from lavage fluid cells was also assessed and the combination of endotoxin, carbon particles, and O_3 produced an increase in oxidant release in old rats. This combination produced the opposite response in the cells recovered from the lungs of the young rats, indicating that the lungs of the aged animals underwent greater oxidative stress in response to this complex pollutant mix of particles, O_3, and a biogenic agent.

Wagner et al. (2001) examined the synergistic effect of co-exposure to O_3 and endotoxin on the transition and respiratory epithelium of rats that also was mediated, in part, by neutrophils. Fisher 344 rats (10 to 12 week old) exposed to 0.5 ppm O_3, 8 h per day, for 3 days, developed mucous cell metaplasia in the nasal transitional epithelium, an area normally devoid of mucous cells; whereas, intratracheal instillation of endotoxin (20 μg) caused mucous cell metaplasia rapidly in the respiratory epithelium of the conducting airways. A synergistic increase of intraepithelial mucosubstances and morphological evidence of mucous cell

metaplasia were found in rat maxilloturbinates upon exposure to both ozone and endotoxin, compared to each pollutant alone.

The effects of O_3 modifying the biological potency of PM (diesel PM and carbon black) was examined by Madden et al. (2000). Reaction of NIST Standard Reference Material # 2975 diesel PM with 0.1 ppm O_3 for 48 hr increased the potency (compared to unexposed or air-exposed diesel PM) to induce neutrophil influx, total protein, and LDH in lung lavage fluid in response to intratracheal instillation. Exposure of the diesel PM to high, non-ambient O_3 concentration (1.0 ppm) attenuated the increased potency, suggesting destruction of the bioactive reaction products. Unlike the diesel particles, carbon black particles exposed to 0.1 ppm O_3 did not exhibit an increase in biological potency, which suggested that the reaction of organic components of the diesel PM with O_3 were responsible for the increased potency. Reaction of particle components with O_3 was ascertained by chemical determination of specific classes of organic compounds.

The interaction of PM and O_3 was further examined in a murine model of ovalbumin (OVA)-induced asthma. Kobzik et al. (2001) investigated whether coexposure to inhaled, concentrated PM from Boston, MA and to O_3 could exacerbate asthma-like symptoms. On days 7 and 14 of life, half of the BALB/c mice used in this study were sensitized by ip injection of OVA and then exposed to OVA aerosol on three successive days to create the asthma phenotype. The other half received the ip OVA, but were exposed to a phosphate-buffered saline aerosol (controls). The mice were further subdivided ($n \geq 61$/group) and exposed for 5 h to CAPs, ranging from 63 to 1,569 $\mu g/m^3$, 0.3 ppm O_3, CAPs + O_3, or to filtered air. Pulmonary resistance and airway responsiveness to an aerosolized MCh challenge were measured after exposures. A small, statistically significant increase in pulmonary resistance and airway responsiveness, respectively, was found in both normal and asthmatic mice immediately after exposure to CAPs alone and to CAPs + O_3, but not to O_3 alone or to filtered air. By 24 h after exposure, the responses returned to baseline levels. There were no significant increases in airway inflammation after any of the pollutant exposures. In this well-designed study of a small-animal model of asthma, O_3 and CAPs did not appear to be synergistic. In further analysis of the data using specific elemental groupings of the CAPs, the acutely increased pulmonary resistance was found to be associated withe the AlSi fraction of PM. Thus, some components of concentrated $PM_{2.5}$ may affect airway caliber in sensitized animals, but the results are difficult to extrapolate to people with asthma.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3 in healthy and asthmatic children. The children performed intermittent exercise during the 4-h exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children, and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to O_3 exposure (Linn et al., 1994; Frampton et al., 1995); and the timing and sequence of the exposures may be important.

Six unique animal studies have examined the adverse cardiopulmonary effects of complex mixtures in urban and rural environments of Italy (Gulisano et al., 1997), Spain (Lorz and Lopez, 1997), and Mexico (Vanda et al., 1998; Calderón-Garcidueñas et al., 2001c,d; Moss et al., 2001). Five of these studies, identified in Table 7-11, have taken advantage of the differences in pollutant mixtures of urban and rural environments to report primarily morphological changes in the nasopharynx (Calderón-Garcidueñas et al., 2001c), the lower respiratory tract (Gulisano et al., 1997; Lorz and Lopez, 1997; Calderón-Garcidueñas et al., 2001c) and in the heart (Calderón-Garcidueñas et al., 2001d) of lambs, pigeons, and dogs, respectively, after natural, continuous exposures to ambient pollution. Each study has provided evidence that animals living in urban air pollutants have greater pulmonary and cardiac changes than would occur in a rural and presumably cleaner, environment. The study by Moss et al. (2001) examined the nasal and lung tissue of rats exposed (23 h/day) to Mexico City air for up to 7 weeks and compared them to controls similarly exposed to filtered air. No inflammatory or epithelial lesions were found using quantitative morphological techniques; however, the concentrations of pollutants were low (see Table 7-11). Extrapolation of these results to humans is restricted, however, by uncontrolled exposure conditions, small sample sizes, and other unknown exposure and nutritional factors in the studies in mammals and birds, and the negative studies in rodents. They also bring up the issue of which species of "sentinel" animals is more useful for predicting pollutant effects in humans. Thus, in these field studies, it is difficult to assign a specific role to

PM (or to any other component of the mixture) in the significant cardiopulmonary effects reported.

Similar morphological changes (Calderón-Garcidueñas et al., 2000a; 2001a,b) and chest X-ray evidence of mild lung hyperinflation (Calderón-Garcidueñas et al., 2000b) have been reported in children residing in urban and rural areas of Mexico City. The ambient air in urban areas, particularly in Southwest Metropolitan Mexico City (SWMMC), is a complex mixture of particles and gases, including high concentrations of O_3 and aldehydes that previously have been shown to cause airway inflammation and epithelial lesions in humans (e.g., Calderón-Garcidueñas et al., 1992, 1994, 1996) and laboratory animals (Morgan et al., 1986; Heck et al., 1990; Harkema et al., 1994, 1997a,b). The described effects demonstrate a persistent, ongoing upper and lower airway inflammatory process and chest X-ray abnormalities in children residing predominantly in SWMMC. Again, extrapolation of these results to urban populations of the United States is difficult because of the complexity of urban air in Mexico City, and the altitude, the uncontrolled exposure conditions, and other unknown exposure and nutritional factors. However, these results may represent an upper bound on what might be the effects of PM in the United States.

Only one controlled study has examined the effect of a combined inhalation exposure to CAPs and O_3 in human subjects. In a randomized, double-blind crossover study, Brook et al. (2002) exposed 25 healthy male and female subjects, 34.9 ± 10 (SD) years of age, to filtered ambient air containing 1.6 $\mu g/m^3$ $PM_{2.5}$ and 9 ppb O_3 (control) or to unfiltered air containing 150 $\mu g/m^3$ CAPs and 120 ppb O_3 while at rest for 2 h. Blood pressure was measured and high-resolution brachial artery ultrasonography was performed prior to and 10 min after exposure. The brachial artery ultrasonography (BAUS) technique was used to measure brachial artery diameter (BAD), endothelium-dependent flow-mediated dilation (FMD), and endothelial-independent nitroglycerine-mediated dilation (NMD). Although no changes in blood pressure or endothelial-dependent or independent dilatation were observed, a small (2.6%) but statistically significant ($p = 0.007$) decrease in BAD was observed in CAPs plus O_3 exposures (−0.09 mm) when compared to filtered air exposures (+0.01 mm). Pre-exposure BAD showed no significant day-to-day variation (0.03 mm), and no significant exposure differences were found for other gaseous pollutants (CO, NO_x, SO_2) in the ambient air. This finding suggests that combined exposure to a mixture of CAPs and O_3 produces vasoconstriction, potentially via autonomic reflexes or as a result of an increase in circulating endothelin, as has been described in rats

exposed to urban PM (Vincent et al., 2001). It is not known, however, whether this effect is caused by CAPS or O_3 alone, or if vasoactive responses would be found at $PM_{2.5}$ and O_3 concentrations typically found in most urban locations in North America.

The effects of gaseous pollutants on PM-mediated responses also have been examined by in vitro studies, though to a limited extent. Churg et al. (1996) demonstrated increased uptake of asbestos or TiO_2 into rat tracheal explant cultures in response to 10 min O_3 (up to 1.0 ppm) pre-exposure. These data suggest that O_3 may increase the penetration of some types of PM into epithelial cells. Additionally, Madden et al. (2000) demonstrated a greater potency for ozonized diesel PM to induce prostaglandin E_2 production from human epithelial cell cultures, suggesting that O_3 can modify the biological activity of PM derived from diesel exhaust.

7.7 SUMMARY OF KEY FINDINGS AND CONCLUSIONS

Toxicological studies can play an integral role in addressing several key issues regarding ambient PM health effects:

(1) What characteristics (size, chemical composition, etc.) of ambient PM cause or contribute to health effects?

(2) What evidence is available for elucidating potential mechanisms underlying PM health effects?

(3) What susceptible subgroups are at increased risk for ambient PM health effects and what types of factors contribute to their increased susceptibility?

(4) What evidence exists that illustrates examples of interactive effects of particles and gaseous copollutants?

This summary focuses on highlighting salient findings that reflect the notable progress that toxicological studies have made towards addressing these questions. All these questions have especially important implications bearing on the issue of biological plausibility of epidemiologically-observed ambient PM effects.

7.7.1 Links Between Specific Particulate Matter Components and Health Effects

Key to the validity of the biological plausibility is the need to understand the linkage between the components of airborne PM responsible for the adverse effects and the individuals at risk. The plausibility of epidemiologically-demonstrated associations between ambient PM and increases in morbidity and mortality has been questioned because adverse cardiopulmonary effects have been observed among human populations at very low ambient PM concentrations. To date, toxicology studies on PM have provided only limited evidence for specific PM components potentially being responsible for observed cardiopulmonary effects of ambient PM. Studies have shown that some components of particles are more toxic than others. For example, high concentrations of ROFA and associated soluble metals have produced clinically significant effects (including death) in compromised animals. The relevance of these findings to understanding the adverse effects of PM components is tempered, however, by the large difference between metal concentrations delivered to the test animals and metal concentrations present in the ambient urban environment. Such comparisons must be applied to the interpretation of all studies that examine the individual components of ambient urban PM. Key findings regrading potential contributions of individual physical/chemical factors of particles to cardiopulmonary effects are summarized below.

7.7.1.2 Acid Aerosols

There is relatively little new information on the effects of acid aerosols, and the conclusions of the 1996 PM AQCD are unchanged. It was previously concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects, but asthmatics may develop small changes in pulmonary function. This conclusion is supported by the recent study of Linn and colleagues (1997) in which children (26 children with allergy or asthma and 15 healthy children) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 h. There were no significant effects on symptoms or pulmonary function when data from the entire group were analyzed, but the allergy group had a significant increase in symptoms after the acid aerosol exposure. Accordingly, acid aerosol health effects may represent a possible causal physical property for PM-related health effects. However, it is unlikely that particle acidity alone could account for the pulmonary function effects (Dreher, 2000).

Although pulmonary effects of acid aerosols have been the subject of extensive research in past decades, the cardiovascular effects of acid aerosols have received little attention. Zhang et al. (1997) reported that inhalation of acetic acid fumes caused reflex-mediated increases in blood pressure in normal and spontaneously hypertensive rats. Thus, acid components should not be ruled out as possible mediators of PM health effects. In particular, the cardiovascular effects of acid aerosols at realistic concentrations need further investigation.

7.7.1.3 Metals

The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) mainly relied on data related to occupational exposures to evaluate the potential toxicity of metals in particulate air pollution. Since that time, newly published in vivo and in vitro studies using ROFA or soluble transition metals have contributed substantial further information on the health effects of particle-associated soluble metals. Although there are some uncertainties about differential effects of one transition metal versus another, water soluble metals leached from ROFA or ambient filter extracts have been shown consistently (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro and in vivo.

Even though it is clear that combustion particles that have a high content of soluble metals can cause lung injury and even death in compromised animals and correlate well with epidemiological findings in some cases (e.g., Utah Valley Studies), it has not been established that the small quantities of metals associated with ambient PM are sufficient to cause health effects. Moreover, it cannot be assumed that metals are the primary toxic component of ambient PM, nor that there is a single primary toxic component. Rather there may be many such components. In studies in which various ambient and emission source particulates were instilled into rats, the soluble metal content did appear to be the primary determinant of lung injury (Costa and Dreher, 1997). However, one published study (Kodavanti et al., 2000a) has compared the effects of inhaled ROFA (at 1 mg/m^3) to concentrated ambient PM (four experiments, at mean concentrations of 475 to 900 $\mu g/m^3$) in normal and SO_2-induced bronchitic rats. A statistically significant increase in at least one lung injury marker was seen in bronchitic rats with only one out of four of the concentrated ambient exposures; whereas inhaled ROFA had no effect, even though the content of soluble iron, vanadium, and nickel was much higher in the ROFA sample than in the concentrated ambient PM.

Nevertheless, particularly interesting new findings point toward ambient PM exacerbation of allergic airway hyperresponsiveness and/or antigen-induced immune responses. Both metal and diesel particles have been implicated with an expanding array of new studies showing DPM in particular as being effective in exacerbating allergic asthmatic responses.

7.7.1.4 Diesel Exhaust Particles

As described in Section 7.5.3, there is growing toxicological evidence that diesel PM exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has been linked to eosinophil degranulation and induction of cytokine production, suggesting that the organic constituents of diesel PM are the responsible part for the immune effects. It is not known whether the adjuvant-like activity of diesel PM is unique or whether other combustion particles have similar effects. It is important to compare the immune effects of other source-specific emissions, as well as concentrated ambient PM, to diesel PM to determine the extent to which exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and asthma.

7.7.1.5 Organic Compounds

Published research on the acute effects of particle-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles. Like metals, organics are common constituents of combustion-generated particles and have been found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial portion of the mass of ambient PM (10 to 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, organic compounds remain a potential causal property for PM health effects due to the contribution of diesel exhaust particles to the fine PM fraction (Dreher, 2000). Strategies have been proposed for examining the health effects of this potentially important constituent (Turpin, 1999).

7.7.1.6 Ultrafine Particles

When this subject was reviewed in the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a), it was not known whether the pulmonary toxicity of freshly generated ultrafine

polytetraflouethylene (PTFE; teflon) particles was due to particle size or a result of adsorbed fumes. Subsequent studies with other ultrafine particles have demonstrated a significantly greater inflammatory response than that seen with fine particles of the same chemical composition at similar mass doses (Oberdorster et al., 1992; Li et al., 1996, 1997, 1999). In other more limited studies, ultrafines also have generated greater oxidative stress in experimental animals. Inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge (100 $\mu g/m^3$ for 6 h) caused minimal lung inflammation per unit mass (Elder et al., 2000a,b), compared to ultrafine PTFE or metal particles. On the other hand, instillation of 125 μg of ultrafine carbon black (20 nm) caused substantially more inflammation per unit mass than did the same dose of fine particles of carbon black (200 to 250 nm), suggesting that ultrafine particles may cause more inflammation per unit mass than larger particles (Li et al., 1997). However, the chemical constituents of the two sizes of carbon black used in this study were not analyzed, and it cannot be assumed that the chemical composition was the same for the two sizes since composition may vary with particle size. Further, when the particle surface area is used a dosimetric, the inflammatory response to both fine and ultrafine particles may be basically the same (Oberdörster, 1996b, 2000; Li et al., 1996). Thus, there is still insufficient toxicological evidence to conclude that ambient concentrations of ultrafine particles contribute to the health effects of particulate air pollution. With acid aerosols, studies of low concentrations of ultrafine sulfuric acid and metal oxide particles have demonstrated effects in the lung. However, it is possible that inhaled ultrafine particles may have systemic effects that are independent of effects on the lung.

7.7.1.7 Concentrated Ambient Particle Studies

Concentrated ambient particle (CAPS) studies should be among the most relevant in helping to understand the characteristics of PM producing toxicity, 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. New particle concentrator systems now coming on-line at the U.S. EPA and elsewhere that permit selective concentration of ultrafine, fine, and thoracic coarse PM hold promise for enhanced understanding of PM characteristics producing toxicity.

7.7.1.8 Bioaerosols

Recent studies support the conclusion of the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a), which stated that bioaerosols, at concentrations present in the ambient environment, would not account for the reported health effects of ambient PM. However, it is possible that bioaerosols could contribute to the health effects of PM. Dose-response studies in healthy volunteers exposed to 0.55 and 50 μg endotoxin, by the inhalation route, showed a threshold for pulmonary and systemic effects for endotoxin between 0.5 and 5.0 μg (Michel et al., 1997). Monn and Becker (1999) examined effects of size fractionated outdoor PM on human monocytes and found cytokine induction characteristic of endotoxin activity in the coarse-size fraction but not in the fine fraction. Available information suggests that ambient concentrations of endotoxin are very low and do not exceed 0.5 ng/m^3. However, there are numerous bioaerosols present in the ambient air including pollens and allergens. Their contribution to the potential health effects of PM are largely unknown.

7.7.2 Mechanisms of Action

The mechanisms that underlie biological responses to ambient PM are not yet clear. Findings since 1996 have provided evidence supporting many hypotheses for PM effects; and this body of evidence has grown substantially. Various toxicologic studies using PM 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. It should be noted that many animal controlled-exposure studies used particle concentrations much higher than those typically occurring in ambient air, whereas clinical concentrator studies have shown responses at levels similar to and higher than those occurring in ambient air (e.g., Ghio et al., 2000a). It is not known if the mechanisms elicited are the same across exposure levels. Clearly, controlled-exposure studies have not as yet been able to delineate fully particle characteristics and the toxicological mechanisms by which ambient PM may affect biological systems. Nevertheless, as discussed in preceding sections of this chapter, much progress has been made since the 1996 PM AQCD in evaluating pathophysiological mechanisms involved in PM-associated cardiovascular and respiratory health effects. Key findings derived from the newly emerging toxicological evidence for these potential pathophysiological mechanisms are summarized below.

7.7.2.1 Direct Pulmonary Effects

When the 1996 PM AQCD was written, the lung was thought to be the primary organ affected by particulate air pollution. Although the lung still is a primary organ affected by PM inhalation, there is growing toxicological and epidemiologic evidence that the cardiovascular system is also affected and may be a co-primary organ system related to certain health endpoints such as mortality. Nonetheless, understanding how particulate air pollution causes or exacerbates respiratory disease remains an important goal. There is some toxicological evidence for the following three hypothesized mechanisms for PM inducing direct pulmonary effects.

Particulate Air Pollution Causes Lung Injury and Inflammation

Particularly compelling evidence pointing towards ambient PM causing lung injury and inflammation derives from the study of ambient PM materials on filter extracts collected from community air monitors before, during the temporary closing of a steel mill in Utah Valley, and after its reopening. Ghio and Devlin (2001) found that intratracheal instillation of filter extract materials in human volunteers provoked greater lung inflammatory responses for materials obtained before and after the temporary closing versus that collected during the plant closing.

The instilled dose of 500 μg of extract material was calculated by Ghio and Devlin to result in focal lung deposition in the lingula roughly equivalent to 5 times more than would be deposited if an active person experienced 24-h inhalation exposure to 100 $\mu g/m^3$ PM_{10} (during wintertime temperature inversions in Utah Valley 24-h PM_{10} levels can exceed 100 $\mu g/m^3$). Moreover, 100 μg of filter extract collected during the winter before the temporary plant closure similarly instilled into the lungs of human volunteers also increased levels of neutrophils, protein, and inflammatory cytokines. Ghio and Devlin (2001) indicated that these results and calculations suggest that biologic effects found in their study could be experienced during a typical winter inversion in the Utah Valley.

Further, the instillation in rats (Dye et al., 2001) of extract materials from before and after the plant closing resulted in a 50% increase in air way hyperresponsiveness to acetylcholine compared to 17 or 25% increases with saline or extract materials for the period when the plant was closed, respectively. Analysis of the extract materials revealed notably greater quantities of metals for when the plant was opened suggesting that such metals (e.g., Cu, Zn, Fe, Pb, As, Mn, Ni) may be important contributors to the pulmonary toxicity observed in the controlled exposure studies, as well as to health effects shown epidemiologically to vary with PM exposures of Utah Valley residents before, during, and after the steel mill closing.

Still other toxicological studies point towards lung injury and inflammation being associated with exposure of lung tissue to complex combustion-related PM materials, with metals again being likely contributors. For example, in the last few years, numerous studies have shown that instilled and inhaled ROFA, a product of fossil fuel combustion, can cause substantial lung injury and inflammation. The toxic effects of ROFA are largely caused by its high content of soluble metals, and some of the pulmonary effects of ROFA can be reproduced by equivalent exposures to soluble metal salts. In contrast, controlled exposures of animals to sulfuric acid aerosols, acid-coated carbon, and sulfate salts cause little lung injury or inflammation, even at high concentrations. Inhalation of concentrated ambient PM (which contains only small amounts of metals) by laboratory animals at concentrations in the range of 100 to 1000 $\mu g/m^3$ have been shown in some (but not all) studies to cause mild pulmonary injury and inflammation. Rats with SO_2-induced bronchitis and monocrotaline-treated rats have been reported to have a greater inflammatory response to concentrated ambient PM than normal rats. These studies suggest that exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

Particulate Air Pollution Causes Increased Susceptibility to Respiratory Infections

Antonini et al. (2002) investigated the effect of preexposure to ROFA on lung defenses and injury after pulmonary challenge with *Listeria monocytogenes*, a bacterial pathogen. Male Sprague-Dawley rats were dosed IT at day 0 with saline (control) or ROFA (0.2 or 1 mg/100 g body weight). Three days later, both groups of rats were instilled IT with a low (5×10^3) or high (5×0^5) dose of *L. monocytogenes*. Chemiluminescence (CL) and nitric oxide (NO) production, two indices of alveolar macrophage (AM) function, were measured on cells recovered from the right lungs by bronchoalveolar lavage. The left lungs and spleens were homogenized, cultured, and colony-forming units were counted after overnight incubation. Exposure to ROFA and the high dose of *L. monocytogenes* led to marked lung injury and inflammation as well as to an increase in mortality, compared with rats treated with saline and the high dose of *L. monocytogenes*. Preexposure to ROFA significantly enhanced injury and delayed the pulmonary clearance of *L. monocytogenes* at both bacterial doses when compared to the saline-treated control rats. ROFA had no effect on AM CL but caused a significant suppression of AM NO production. The authors concluded that acute exposure to ROFA slowed pulmonary clearance of *L. monocytogenes* and altered AM function. They postulated that these changes could lead to increased susceptibility to lung infection in exposed populations.

Ohtsuka et al. (2000a,b) have also shown that a single 4 h exposure of mice to acid-coated carbon particles at a mass concentration of 10,000 $\mu g/m^3$ carbon black causes decreased phagocytic activity of alveolar macrophages, even in the absence of lung injury.

Particulate Air Pollution Increases Airway Reactivity and Exacerbates Asthma

The strongest evidence supporting this hypothesis is from studies on diesel particulate matter (DPM). Diesel particulate matter has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 7.2.1.2). In vitro studies have suggested that the organic fraction of DPM is involved in the increased IgE production. ROFA leachate also has been shown to enhance antigen-specific airway reactivity in mice (Goldsmith et al., 1999), indicating that soluble metals can also enhance an allergic response. However, in this same study, exposure of mice to concentrated ambient PM did not affect antigen-specific airway reactivity. It is premature to conclude from the Goldsmith experiment that concentrated ambient PM does not exacerbate allergic airways disease because the chemical composition of

the PM (as indicated by studies with DPM and ROFA) may be more important than the mass concentration.

7.7.2.2 Systemic Effects Secondary to Lung Injury

When the 1996 PM AQCD was written, it was thought that cardiovascular-related morbidity and mortality most likely would be secondary to impairment of oxygenation or some other consequence of lung injury and inflammation. Newly available toxicologic studies provide some additional evidence regarding such possibilities.

Lung Injury from Inhaled Particulate Matter Causes Impairment of Oxygenation and Increased Work of Breathing That Adversely Affects the Heart

Instillation of ROFA (0, 0.25, 1.0, 2.5 mg) has been shown to cause a 50% mortality rate in monocrotaline-treated rats (Watkinson et al., 2000a,b). Although blood oxygen levels were not measured in this study, there were ECG abnormalities consistent with severe hypoxemia in about half of the rats that subsequently died. Given the severe inflammatory effects of instilled ROFA and the fact that monocrotaline-treated rats have increased lung permeability as well as pulmonary hypertension, it is plausible that instilled ROFA can cause severe hypoxemia leading to death in this rat model. Results from studies in which animals (normal and compromised) were exposed to concentrated ambient PM (at concentrations many times higher than would be encountered in the United States) indicate that ambient PM is unlikely to cause severe disturbances in oxygenation or pulmonary function. However, even a modest decrease in oxygenation can have serious consequences in individuals with ischemic heart disease. Kleinman et al. (1998) has shown that a reduction in arterial blood saturation from 98 to 94% by either mild hypoxia or by exposure to 100 ppm CO significantly reduced the time to onset of angina in exercising volunteers. Thus, information is needed on the effects of PM on arterial blood gases and pulmonary function to fully address the above hypothesis.

Lung Inflammation and Cytokine Production Cause Adverse Systemic Hemodynamic Effects

It has been suggested that systemic effects of particulate air pollution may result from activation of cytokine production in the lung (Li et al., 1997). In support of this idea, monocrotaline-treated rats exposed to inhaled ROFA (15,000 $\mu g/m^3$, 6 h/day for 3 days) showed increased pulmonary cytokine gene expression, bradycardia, hypothermia, and increased

arrhythmias (Watkinson et al., 2000a,b). However, spontaneously hypertensive rats had a similar cardiovascular response to inhaled ROFA (except that they also developed ST segment depression) with no increase in pulmonary cytokine gene expression. Studies in dogs exposed to concentrated ambient PM (322 μg/m^3, MMAD = 0.23-.034 μm) showed minimal pulmonary inflammation and no positive staining for IL-8, IL-1, or TNF in airway biopsies. However, there was a significant decrease in the time of onset of ischemic ECG changes following coronary artery occlusion in PM-exposed dogs compared to controls (Godleski et al., 2000). Thus, the link between changes in the production of cytokines in the lung and cardiovascular function is not clear-cut, and basic information on the effects of mild pulmonary injury on cardiovascular function is needed to understand the mechanisms by which inhaled PM affects the heart. In this regard, Wellenius et al. (2002) have developed and tested a model for investigating the effects of inhaled PM on arrhythmias and heart rate variability (HRV) in rats with acute myocardial infarction. Left-ventricular MI was induced in Sprague-Dawley rats by thermocoagulation of the left coronary artery. Diazepam-sedated rats were exposed (1 h) to residual oil fly ash (ROFA), carbon black, or room air at 12-18 h after surgery. Each exposure was immediately preceded and followed by a 1-h exposure to room air (baseline and recovery periods, respectively). Lead-II electrocardiograms were recorded. In the MI group, 41% of rats exhibited one or more premature ventricular complexes (PVCs) during the baseline period. Exposure to ROFA, but not to carbon black or room air, increased arrhythmia frequency in animals with preexisting PVCs. Furthermore, MI rats exposed to ROFA, but not to carbon black or room air, decreased HRV. There was no difference in arrhythmia frequency or HRV among sham-operated animals. The authors concluded that this model may be useful for elucidating the physiologic mechanisms of particle-induced cardiovascular arrhythmias and contribute to defining the specific constituents of ambient particles responsible for arrhythmias.

Lung Inflammation from Inhaled Particulate Matter Causes Increased Blood Coagulability That Increases the Risk of Heart Attacks and Strokes

There is abundant evidence linking risk of heart attacks and strokes to small prothrombotic changes in the blood coagulation system. However, the published toxicological evidence that moderate lung inflammation causes increased blood coagulability is inconsistent. Ghio et al. (2000a) have shown that inhalation of concentrated ambient PM in healthy nonsmokers causes increased levels of blood fibrinogen. Gardner et al. (2000) have shown that a high dose

(8,300 μg/kg) of instilled ROFA in rats causes increased levels of fibrinogen, but no effect was seen at lower doses. Exposure of dogs to concentrated ambient PM had no effect on fibrinogen levels (Godleski et al., 2000). The coagulation system is as multifaceted and complex as the immune system, and there are many other sensitive and clinically significant parameters that should be examined in addition to fibrinogen. Thus, it is premature to draw any conclusions about the relationship between PM and blood coagulation.

Interaction of Particulate Matter with the Lung Affects Hematopoiesis

Terashima et al. (1997) found that instillation of fine carbon particles (20,000 μg/rabbit) stimulated release of PMNs from bone marrow. In further support of this hypothesis, Gordon and colleagues reported that the percentage of PMNs in the peripheral blood increased in rats exposed to ambient PM in some but not all exposures. On the other hand, Godleski et al. (2000) found no changes in peripheral blood counts of dogs exposed to concentrated ambient PM. Thus, consistent evidence that PM ambient concentrations can affect hematopoiesis remains to be demonstrated.

7.7.2.3 Direct Effects on the Heart

Changes in heart rate, heart rate variability, and conductance associated with ambient PM exposure have been reported in animal studies (Godleski et al., 2000; Gordon et al., 2000; Watkinson et al., 2000a,b; Campen et al., 2000), in several human panel studies (described in Chapter 8), and in a reanalysis of data from the MONICA study (Peters et al., 1997). Some of these studies included endpoints related to respiratory effects but few significant adverse respiratory changes were detected. This raises the possibility that ambient PM may have effects on the heart that are independent of adverse changes in the lung. There is certainly precedent for this idea. For example, tobacco smoke (which is a mixture of combustion-generated gases and PM) causes cardiovascular disease by mechanisms that are independent of its effect on the lung. Two types of hypothesized direct effects of PM on the heart are noted below.

Inhaled Particulate Matter Affects the Heart by Uptake of Particles into the Circulation or Release of a Soluble Substances into the Circulation

Drugs can be rapidly and efficiently delivered to the systemic circulation by inhalation. This implies that the pulmonary vasculature absorbs inhaled materials, including charged

substances such as small proteins and peptides. Nemmar et al. (2001) studied the movement of radioactively labeled ultrafine particles out of the lungs of hamsters receiving a single IT instillation of albumin nanocolloid particles (≤80 nm) labeled with ^{99m}Tc and killed after 5, 15, 30, and 60 min. Blood radioactivity, at 5, 15, 30, and 60 min, respectively, expressed as percentage of total body radioactivity per gram blood, was 2.88 ± 0.80%, 1.30 ± 0.17%, 1.52 ± 0.46%, and 0.21 ± 0.06%. Liver radioactivity, at 5, 15, 30, and 60 min, respectively, expressed as percentage of total radioactivity per organ, was 0.10 ± 0.07%, 0.23 ± 0.06%, 1.24 ± 0.27%, and 0.06 ± 0.02%. Lower values were observed in the heart, spleen, kidneys, and brain. Dose dependence was assessed at 30 min following instillation of 10 μg and 1 μg ^{99m}Tc-albumin per animal (n = 3 at each dose), and values of the same relative magnitudes as after instillation of 100 μg were obtained. The authors concluded that a significant fraction of ultrafine ^{99m}Tc-albumin diffuses rapidly from the lungs into the systemic circulation.

Nemmar et al. (2002) investigated the extent inhaled particles entered into the systemic circulation, in 5 healthy volunteers, after inhaling "Technegas," an aerosol consisting mainly of ultrafine ^{99m}Tc -labeled carbon particles (< 100 nm). Radioactivity detected in blood at 1 minute, reached a maximum between 10 and 20 minutes, and remained at this level up to 60 minutes. Thin layer chromatography of blood showed that in addition to a species corresponding to oxidized ^{99m}Tc (i.e., pertechnetate) there was also a species corresponding to particle-bound ^{99m}Tc. Gamma camera images showed substantial radioactivity over the liver and other areas of the body. These workers conclude that inhaled ^{99m}Tc-labeled ultrafine carbon particles pass rapidly into the systemic circulation.

Inhaled Particulate Matter Affects Autonomic Control of the Heart and Cardiovascular System

There is growing evidence for this idea as described above. This raises the question of how inhaled particles could affect the autonomic nervous system. Activation of neural receptors in the lung is a logical area to investigate. Studies in conscious rats have shown that inhalation of wood smoke causes marked changes in sympathetic and parasympathetic input to the cardiovascular system that are mediated by neural reflexes (Nakamura and Hayashida, 1992). Although research on airway neural receptors and neural-mediated reflexes is a well established discipline, the cardiovascular effects of stimulating airway receptors continue to receive less attention than the pulmonary effects. Previous studies of airway reflex-mediated cardiac effects

usually employed very high doses of chemical irritants, and the results may not be applicable to air pollutants. There is a need for basic physiological studies to examine effects on cardiovascular system when airway and alveolar neural receptors are stimulated in a manner relevant to air pollutants.

7.7.3 Susceptibility

Progress has been made in understanding the role of individual susceptibility to ambient PM effects. Studies have consistently shown that older animals or animals with certain types of compromised health, either genetic or induced, are more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models has created greater uncertainty for the interpretation of the findings (Clarke et al., 1999, 2000; Kodavanti et al., 1998, 2000b, 2001; Gordon et al., 2000; Ohtsuka et al., 2000c; Wesselkamper et al., 2000; Leikauf et al., 2000; Saldiva et al., 2002). Moreover, because PM seems to affect broad categories of disease states, ranging from cardiac arrhythmias to pulmonary infection, it can be difficult to know what disease models to use in evaluating the biological plausibility of adverse health effects of PM.

Nevertheless, particularly interesting new findings point toward ambient PM exacerbation of allergic airway hyperresponsiveness and/or antigen-induced immune responses. Both metals and diesel particles have been implicated, with an expanding array of new studies showing DPM in particular as being effective in exacerbating allergic asthma responses (Takano et al., 1997; Nel et al., 2001; Van Zijverden et al., 2000, 2001; Walters et al., 2001; Nordenhall et al., 2001; Hamada et al., 1999, 2000; Lambert et al., 1999; Gilmour et al., 2001).

7.7.4 PM Interactions with Gaseous Co-Pollutants

Several new studies have examined possible cardiopulmonary effects of complex air pollution mixtures in Mexico, Spain, and Italy. These studies, taking advantage of differences in pollutant mixtures and concentrations in relatively "clean" rural areas versus urban environments found morphological changes in the nasopharynx (Calderón-Garcidueñas et al., 2001c), the lower respiratory tract (Gulisano et al., 1997; Lorz and Lopez, 1997; Calderón-Garcidueñas et al., 2001c) and in the heart (Calderón-Garcidueñas et al., 2001c) of lambs, pigeons, and dogs, respectively, experiencing long-term continuous natural exposures to elevated ambient air pollution. Each study provided evidence suggesting that animals living in urban environments

with higher air pollution levels have greater pulmonary and cardiac changes than those living in cleaner rural areas. It is difficult, however, to (a) assign relative specific roles to PM or other components of the urban air mixtures in producing the observed effects or (b) extrapolate the findings to U.S. urban situations having typically much lower air pollutant concentrations (e.g. especially the case for notably higher PM and O_3 levels observed in Mexico City than in U.S. cities).

Two well-conducted new controlled human exposure studies do provide somewhat more readily interpretable results. In one, a randomized double-blind crossover study by Brook et al. (2002) observed increased brachial artery constriction in adult males and females, mean age = 34.9 yr ± 10 SD, exposed for 2 hr to filtered ambient air containing 150 $\mu g/m^3$ CAPS and 120 ppb O_3 while at rest. Another study, by Linn et al. (1997) found a positive association between acid concentration and respiratory symptoms (but not spirometry) among asthmatic children following a single 4-hr exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3 while undergoing intermittent exercise. No changes were seen among healthy children.

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.

Alink, G. M.; Sjögren, M.; Bos, R. P.; Doekes, G.; Kromhout, H.; Scheepers, P. T. J. (1998) Effect of airborne particles from selected indoor and outdoor environments on gap-junctional intercellular communication. Toxicol. Lett. 96/97: 209-213.

Amdur, M. O.; Chen, L. C. (1989) Furnace-generated acid aerosols: speciation and pulmonary effects. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 147-150.

Amdur, M. O.; Dubriel, M.; Creasia, D. A. (1978) Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

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.

Brightwell, J.; Fouillet, X.; Cassano-Zoppi, A.-L.; Gatz, R.; Duchosal, F. (1986) Neoplastic and functional changes in rodents after chronic inhalation of engine exhaust emissions. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 471-485. (Developments in toxicology and environmental science: v. 13).

Broeckaert, F.; Buchet, J. P.; Huaux, F.; Lardot, C.; Lison, D.; Yager, J. W. (1997) Reduction of the ex vivo production of tumor necrosis factor alpha by alveolar phagocytes after administration of coal fly ash and copper smelter dust. J. Toxicol. Environ. Health 51: 189-202.

Brook, R. D.; Brook, J. R.; Urch, B.; Vincent, R.; Rajagopalan, S.; Silverman, F. (2002) Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in health adults. Circulation 105: 1534-1536.

Bünger, J.; Krahl, J.; Baum, K.; Schröder, O.; Müller, M.; Westphal, G.; Ruhnau, P.; Schulz, T. G.; Hallier, E. (2000) Cytotoxic and mutagenic effects, particle size and concentration analysis of diesel engine emissions using biodiesel and petrol diesel as fuel. Arch. Toxicol. 74: 490-498.

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.; 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.

California Environmental Protection Agency. (1998) Report to the Air Resources Board on the proposed identification of diesel exhaust as a toxic air contaminant. Part A: exposure assessment. Sacramento, CA: Air Resources Board. Available: http://www.arb.ca.gov/regact/diesltac/diesltac.htm [16 May, 2003].

Campen, M. J.; Costa, D. L.; Watkinson, W. P. (2000) Cardiac and thermoregulatory toxicity of residual oil fly ash in cardiopulmonary-compromised rats. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 7-22.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Evansky, P. A.; Costa, D. L.; Watkinson, W. P. (2001) Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol. Sci. 64: 243-252.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Costa, D. L.; Watkinson, W. P. (2002) Cardiac and thermoregulatory effects of instilled particulate matter-associated transition metals in healthy and cardiopulmonary-compromised rats. J. Toxicol. Environ. Health Part A 65:1615-1631.

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. (2000b) 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.

Clarke, R. W.; Antonini, J. M.; Hemenway, D. R.; Frank, R.; Kleeberger, S. R.; Jakab, G. J. (2000c) Inhaled particle-bound sulfate: effects on pulmonary inflammatory responses and alveolar macrophage function. Inhalation Toxicol. 12: 169-186.

Cohen, M. D.; Becker, S.; Devlin, R.; Schlesinger, R. B.; Zelikoff, J. T. (1997) Effects of vanadium upon polyI:C-induced responses in rat lung and alveolar macrophages. J. Toxicol. Environ. Health 51: 591-608.

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.

Diociaiuti, M.; Balduzzi, M.; De Berardis, B.; Cattani, G.; Stacchini, G.; Ziemacki, G.; Marconi, A.; Paoletti, L. (2001) The two $PM_{2.5}$ (fine) and $PM_{2.5\text{-}10}$ (coarse) fractions: evidence of different biological activity. Environ. Res. A 86: 254-262.

Donaldson, K.; Brown, D. M.; Mitchell, C.; Dineva, M.; Beswick, P. H.; Gilmour, P.; MacNee, W. (1997) Free radical activity of PM_{10}: iron-mediated generation of hydroxyl radicals. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1285-1289.

Dong, W.; Lewtas, J.; Luster, M. I. (1996) Role of endotoxin in tumor necrosis factor α expression from alveolar macrophages treated with urban air particles. Exp. Lung Res. 22: 577-592.

Dormans, J. A. M. A.; Steerenberg, P. A.; Arts, J. H. E.; Van Bree, L.; De Klerk, A.; Verlaan, A. P. J.; Bruijntjes, J. P.; Beekhof, P.; Van Soolingen, D.; Van Loveren, H. (1999) Pathological and immunological effects of respirable coal fly ash in male wistar rats. Inhalation Toxicol. 11: 51-69.

Dreher, K. L. (2000) Particulate matter physicochemistry and toxicology: in search of causality — a critical perspective. Inhalation Toxicol. 12(suppl. 3): 45-57.

Dreher, K. L.; Jaskot, R. H.; Lehmann, J. R.; Richards, J. H.; McGee, J. K.; Ghio, A. J.; Costa, D. L. (1997) Soluable transition metals mediate residual oil fly ash induced acute lung injury. J. Toxicol. Environ. Health 50: 285-305.

Driscoll, K. E.; 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. Suppl. 109(3): 395-403.

Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000a) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 85-98.

Elder, A. C. P.; Gelein, R.; Finkelstein, J. N.; Cox, C.; Oberdörster, G. (2000b) Pulmonary inflammatory response to inhaled ultrafine particles is modified by age, ozone exposure, and bacterial toxin. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 227-246.

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. (2001) Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. Environ. Health Perspect. 109(suppl. 4): 529-532.

Frampton, M. W.; Voter, K. Z.; Morrow, P. E.; Roberts, N. J., Jr.; Culp, D. J.; Cox, C.; Utell, M. J. (1992) Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. Am. Rev. Respir. Dis. 146: 626-632.

Frampton, M. W.; Morrow, P. E.; Cox, C.; Levy, P. C.; Condemi, J. J.; Speers, D.; Gibb, F. R.; Utell, M. J. (1995) Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. Environ. Res. 69: 1-14.

Frampton, M. W.; Ghio, A. J.; Samet, J. M.; Carson, J. L.; Carter, J. D.; Devlin, R. B. (1999) Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. Am. J. Physiol. 277: L960-L967.

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.; Richards, J. H.; Dittrich, K. L.; Samet, J. M. (1998a) Metal storage and transport proteins increase after exposure of the rat lung to an air pollution particle. Toxicol. Pathol. 26: 388-394.

Ghio, A. J.; Carter, J. D.; Richards, J. H.; Brighton, L. E.; Lay, J. C.; Devlin, R. B. (1998b) Disruption of normal iron homeostasis after bronchial instillation of an iron-containing particle. Am. J. Physiol. 274: L396-L403.

Ghio, A. J.; Carter, J. D.; Samet, J. M.; Reed, W.; Quay, J.; Dailey, L. A.; Richards, J. H.; Devlin, R. B. (1998c) Metal-dependent expression of ferritin and lactoferrin by respiratory epithelial cells. Am. J. Physiol. 274: L728-L736.

Ghio, A. J.; Stonehuerner, J.; Dailey, L. A.; Carter, J. D. (1999a) Metals associated with both the water-soluble and insoluble fractions of an ambient air pollution particle catalyze an oxidative stress. Inhalation Toxicol. 11: 37-49.

Ghio, A. J.; Carter, J. D.; Dailey, L. A.; Devlin, R. B.; Samet, J. M. (1999b) Respiratory epithelial cells demonstrate lactoferrin receptors that increase after metal exposure. Am. J. Physiol. 276: L933-L940.

Ghio, A. J.; Stoneheurner, J.; McGee, J. K.; Kinsey, J. S. (1999c) Sulfate content correlates with iron concentrations in ambient air pollution particles. Inhalation Toxicol. 11: 293-307.

Ghio, A. J.; Kim, C.; Devlin, R. B. (2000a) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am. J. Respir. Crit. Care Med. 162: 981-988.

Ghio, A. J.; Richards, J. H.; Carter, J. D.; Madden, M. C. (2000b) Accumulation of iron in the rate lung after tracheal instillation of diesel particles. Toxicol. Pathol. 28: 619-627.

Ghio, A. J.; Carter, J. D.; Richards, J. H.; Crissman, K. M.; Bobb, H. H.; Yang, F. (2000c) 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.

Hamers, T.; Van Schaardenburg, M. D.; Felzel, E. C.; Murk, A. J.; Koeman, J. H. (2000) The application of reporter gene assays for the determination of the toxic potency of diffuse air pollution. Sci. Total Environ. 262: 159-174.

Harder, S. D.; Soukup, J. M.; Ghio, A. J.; Devlin, R. B.; Becker, S. (2001) Inhalation of $PM_{2.5}$ does not modulate host defense or immune parameters in blood or lung of normal human subjects. Environ. Health Perspect. Suppl. 109(4): 599-604.

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.

Heinrich, U.; Peters, L.; Funcke, W.; Pott, F.; Mohr, U.; Stöber, W. (1982) Investigation of toxic and carcinogenic effects of diesel exhaust in long-term inhalation exposure of rodents. In: Lewtas, J., ed. Toxicological effects of emissions from diesel engines: proceedings of the Environmental Protection Agency diesel emissions symposium; October 1981; Raleigh, NC. New York, NY: Elsevier Biomedical; pp. 225-242. (Developments in toxicology and environmental science: v. 10).

Heinrich, U.; Muhle, H.; Takenaka, S.; Ernst, H.; Fuhst, R.; Mohr, U.; Pott, F.; Stöber, W. (1986) Chronic effects on the respiratory tract of hamsters, mice, and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. J. Appl. Toxicol. 6: 383-395.

Heinrich, U.; Fuhst, R.; Rittinghausen, S.; Creutzenberg, O.; Bellmann, B.; Koch, W.; Levsen, K. (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titantium dioxide. Inhalation Toxicol. 7: 533-556.

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.

Hornberg, C.; Maciuleviciute, L.; Seemayer, N. H. (1996) Sister chromatid exchanges in rodent tracheal epithelium exposed in vitro to environmental pollutants. Toxicol. Lett. 88: 45-53.

Hornberg, C.; Maciuleviciute, L.; Seemayer, N. H.; Kainka, E. (1998) Induction of sister chromatid exchanges (SCE) in human tracheal epithelial cells by the fractions PM-10 and PM-2.5 of airborne particulates. Toxicol. Lett. 96/97: 215-220.

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.

Iwai, K.; Udagawa, T.; Yamagishi, M.; Yamada, H. (1986) Long-term inhalation studies of diesel exhaust on F344 SPF rats. Incidence of lung cancer and lymphoma. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 349-360. (Developments in toxicology and environmental science: v. 13).

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/Kobzik.pdf [27 January 2003].

Kodavanti, U. P.; Costa, D. L. (1999) Animal models to study for pollutant effects. In: Holgate, S. T.; Samet, J. M.; Koren, H. S.; Maynard, R. L., eds. Air pollution and health. New York, NY: Academic Press; pp. 165-197.

Kodavanti, U. P.; Jaskot, R. H.; Bonner, J.; Badgett, A.; Dreher, K. L. (1996) Eosinophilic lung inflammation in particulate-induced lung injury: technical consideration in isolating RNA for gene expression studies. Exp. Lung Res. 22: 541-554.

Kodavanti, U. P.; Jaskot, R. H.; 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. Suppl. 106(1): 111-130.

Kodavanti, U. P.; Jackson, M. C.; Ledbetter, A. D.; Richards, J. R.; Gardner, S. Y.; Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1999) Lung injury from intratracheal and inhalation exposures to residual oil fly ash in a rat model of monocrotaline-induced pulmonary hypertension. J. Toxicol. Environ. Health Part A 57: 101-121.

Kodavanti, U. P.; 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 Part A 65: 1545-1569.

Kuschner, W. G.; D'Alessandro, A.; Wintermeyer, S. F.; Wong, H.; Boushey, H. A.; Blanc, P. D. (1995) Pulmonary responses to purified zinc oxide fume. J. Invest. Med. 43: 371-378.

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-research.htm [15 May, 2003].

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.

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.

Molinelli, A. R.; Madden, M. C.; McGee, J. K.; Stonebuerner, J. G.; Ghio, A. J. (2002) Effect of metal removal on the toxicity of airborne particulate matter from the Utah Valley. Inhalation Toxicol. 14: 1069-1086.

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/pubs-research.htm [15 May, 2003].

Muggenburg, B. A.; Barr, E. B.; Cheng, Y. S.; Seagrave, JC.; Tilley, L. P.; Mauderly, J. L. (2000a) Effect of inhaled residual oil fly ash on the electrocardiogram of dogs. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 189-208.

Muggenburg, B. A.; Tilley, L.; Green, F. H. Y. (2000b) Animal models of cardiac disease: potential usefulness for studying health effects of inhaled particles. Inhalation Toxicol. 12: 901-925.

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 Part A 65:1333-1350.

Nadadur, S. S.; Schladweiler, M. C. J.; Kodavanti, U. P. (2000) A pulmonary rat gene array for screening altered expression profiles in air pollutant-induced lung injury. Inhalation Toxicol. 12: 1239-1254.

Nadeau, D.; Vincent, R.; Kumarathasan, P.; Brook, J.; Dufresne, A. (1996) Cytotoxicity of ambient air particles to rat lung macrophages: comparison of cellular and functional assays. Toxicol. in Vitro 10: 161-172.

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.

Nel, A. E.; Diaz-Sanchez, D.; Li, N. (2001) The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr. Opin. Pulm. Med. 7: 20-26.

Nemmar, A.; Delaunois, A.; Nemery, B.; Dessy-Doizé, C.; Beckers, J.-F.; Sulon, J.; Gustin, P. (1999) Inflammatory effect of intratracheal instillation of ultrafine particles in the rabbit: role of C-fiber and mast cells. Toxicol. Appl. Pharmacol. 160: 250-261.

Nemmar, A.; 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, P. 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.

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. (1996a) Effects of ultrafine particles in the lung and potential relevance to environmental particles. In: Marijnissen, J. C. M.; Gradon, L., eds. Proceedings of Aerosol inhalation, lung transport, deposition and the relation to the environment: recent research frontiers, an international workshop; September,1995; Warsaw, Poland. London, United Kingdom: Kluwer Academic; pp. 165-174.

Oberdörster, G. (1996b) Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Inhalation Toxicol. 8(suppl.): 73-89.

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

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

Oberdörster, G.; Finkelstein, J. N.; Johnston, C.; Gelein, R.; Cox, C.; Baggs, R.; Elder, A. C. P. (2000) Acute pulmonary effects of ultrafine particles in rats and mice. Cambridge, MA: Health Effects Institute; research report no. 96.

Oettinger, R.; Drumm, K.; Knorst, M.; Krinyak, P.; Smolarski, R.; Kienast, K. (1999) Production of reactive oxygen intermediates by human macrophages exposed to soot particles and asbestos fibers and increase in NF-kappa B p50/p105 mRNA. Lung 177: 343-354.

Ohtoshi, T.; Takizawa, H.; Okazaki, H.; Kawasaki, S.; Takeuchi, N.; Ohta, K.; Ito, K. (1998) Diesel exhaust particles stimulate human airway epithelial cells to produce cytokines relevant to airway inflammation *in vitro*. J. Allergy Clin. Immunol. 101: 778-785.

Ohtsuka, Y.; Clarke, R. W.; Mitzner, W.; Brunson, K.; Jakab, G. J.; Kleeberger, S. R. (2000a) Interstrain variation in murine susceptibility to inhaled acid-coated particles. Am. J. Physiol. L469-L476.

Ohtsuka, Y.; Brunson, K. J.; Jedlicka, A. E.; Mitzner, W.; Clarke, R. W.; Zhang, L.-Y.; Eleff, S. M.; Kleeberger, S. R. (2000b) Genetic linkage analysis of susceptibility to particle exposure in mice. Am. J. Respir. Cell Mol. Biol. 22: 574-581.

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.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Prahalad, A. K.; Soukup, J. M.; Inmon, J.; Willis, R.; Ghio, A. J.; Becker, S.; Gallagher, J. E. (1999) Ambient air particles: effects on cellular oxidant radical generation in relation to particulate elemental chemistry. Toxicol. Appl. Pharmacol. 158: 81-91.

Pritchard, R. J.; Ghio, A. J.; Lehmann, J. R.; Winsett, D. W.; Tepper, J. S.; Park, P.; Gilmour, M. I.; Dreher, K. L.; Costa, D. L. (1996) Oxidant generation and lung injury after particulate air pollutant exposure increase with the concentrations of associated metals. Inhalation Toxicol. 8: 457-477.

Prows, D. R.; 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.; Stjernberg, N.; Kolmodin-Hedman, B. (1990) Controlled diesel exhaust exposure in an exposure chamber: pulmonary effects investigated with bronchoalveolar lavage. J. Aerosol Sci. 21(suppl. 1): S411-S414.

Rudell, B.; Sandström, T.; Hammarström, U.; Ledin, M.-L.; Hörstedt, P.; Stjernberg, N. (1994) Evaluation of an exposure setup for studying effects of diesel exhaust in humans. Int. Arch. Occup. Environ. Health 66: 77-83.

Rudell, B.; Ledin, M.-C.; Hammarström, U.; Stjernberg, N.; Lundbäck, B.; Sandström, T. (1996) Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. Occup. Environ. Med. 53: 658-662.

Rudell, B.; Blomberg, A.; Helleday, R.; Ledin, M.-C.; Lundbäck, B.; Stjernberg, N.; Hörstedt, P.; Sandström, T. (1999) Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. Occup. Environ. Med. 56: 527-534.

Sagai, M.; Furuyama, A.; Ichinose, T. (1996) Biological effects of diesel exhaust particles (DEP). III. Pathogenesis of asthma like symptoms in mice. Free Radical Biol. Med. 21: 199-209.

Saldiva, P. H. N.; Clarke, R. W; Coull, B. A.; Stearns, R. C.; Lawrence, J.; Krishna-Murthy, G. G.; Diaz, E.; Koutrakis, P.; Suh, H.; Tsuda, A.; Godleski, J. J. (2002) Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am. J. Respir. Crit. Care Med. 165: 1610-1617.

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.

Seemayer, N. H.; Hornberg, C. (1998) Malignant transformation of Syrian hamster kidney cells in vitro by interaction of airborne particulates and simian virus (SV-) 40. Toxicol. Lett. 96/97: 231-238.

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.; Becker, S. (2001) Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. Toxicol. Appl. Pharmacol. 171: 20-26.

Soukup, J. M.; Ghio, A. J.; Becker, S. (2000) Soluble components of Utah Valley particulate pollution alter alveolar macrophage function in vivo and in vitro. Inhalation Toxicol. 12: 401-414.

Spengler, J. D.; Thurston, G. D. (1983) Mass and elemental composition of fine and coarse particles in six U.S. cities. J. Air Pollut. Control Assoc. 33: 1162-1171.

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.

Stöber, W. (1986) Experimental induction of tumors in hamsters, mice and rats after long-term inhalation of filtered and unfiltered diesel engine exhaust. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, The Netherlands: Elsevier Science Publishers B. V.; pp. 421-439. (Developments in toxicology and environmental science: v. 13).

Stringer, B.; Kobzik, L. (1996) Alveolar macrophage uptake of the environmental particulate titanium dioxide: role of surfactant components. Am. J. Respir. Cell Mol. Biol. 14: 155-160.

Stringer, B.; Kobzik, L. (1998) Environmental particulate-mediated cytokine production in lung epithelial cells (A549): role of preexisting inflammation and oxidant stress. J. Toxicol. Environ. Health Part A 55: 31-44.

Stringer, B.; Imrich, A.; Kobzik, L. (1996) Lung epithelial cell (A549) interaction with unopsonized environmental particulates: quantitation of particle-specific binding and IL-8 production. Exp. Lung Res. 22: 495-508.

Su, W.-Y.; Jaskot, R. H.; Richards, J.; Abramson, S. R.; Woessner, J. F., Jr.; Yu, W.-H.; Dreher, K. L. (2000a) Induction of pulmonary matrilysin expression by combustion and ambient air particles. Am. J. Physiol. 279: L152-L160.

Su, W.-Y.; Jaskot, R. H.; Dreher, K. L. (2000b) Particulate matter induction of pulmonary gelatinase A, gelatinase B, tissue inhibitor of metalloproteinase expression. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 105-119.

Sun, G.; Crissman, K.; Norwood, J.; Richards, J.; Slade, R.; Hatch, G. E. (2001) Oxidative interactions of synthetic lung epithelial lining fluid with metal-containing particulate matter. Am. J. Physiol. 281: L807-L815.

Suwa, T.; Hogg, J. C.; Quinlan, K. B.; Ohgami, A.; Vincent, R.; Van Eeden, S. F. (2002) Particulate air pollution induces progression of atherosclerosis. J. Am. Coll. Cardiol. 39: 935-942.

Takano, H.; Yoshikawa, T.; Ichinose, T.; Miyabara, Y.; Imaoka, K.; Sagai, M. (1997) Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. Am. J. Respir. Crit. Care Med. 156: 36-42.

Takano, H.; Ichinose, T.; Miyabara, Y.; Shibuya, T.; Lim, H.-B.; Yoshikawa, T. Sagai, M. (1998) Inhalation of diesel exhaust enhances allergen-related eosinophil recruitment and airway hyperresponsiveness in mice. Toxicol. Appl. Pharmacol. 150: 328-337.

Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The human bone marrow response to acute air pollution caused by forest fires. Am. J. Respir. Crit. Care Med. 161: 1213-1217.

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. (1999) Discussion paper for CASAC-diesel health assessment issues. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; paper no. NCEA-W-0634. Available: http://cfpub.epa.gov/ncea/ [16 May, 2003].

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. (2000) Adjuvant activity of particulate pollutants in different mouse models. Toxicology 152: 69-77.

Van Zijverden, M.; Van der Pijl, A.; Bol, M.; Van Pinxteren, F. A.; De Haar, C.; Penninks, A. H.; Van Loveren, H.; Pieters, R. (2000) Diesel exhaust, carbon black, and silica particles display distinct Th1/Th2 modulating activity. Toxicol. Appl. Pharmacol. 168: 131-139.

Van Zijverden, M.; De Haar, C.; Van Beelen, A.; Van Loveren, H.; Penninks, A.; Pieters, R. (2001) Co-administration of antigen and particles optimally stimulates the immune response in an intranasal administration model in mice. Toxicol. Appl. Pharmacol. 177: 174-178.

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.; Oortgiesen, M.; Carter, J. D.; Devlin, R. B. (1999a) Particulate matter initiates inflammatory cytokine release by activation of capsaicin and acid receptors in a human bronchial epithelial cell line. Toxicol. Appl. Pharmacol. 154: 106-115.

Veronesi, B.; Carter, J. D.; Devlin, R. B.; Simon, S. A.; Oortgiesen, M. (1999b) Neuropeptides and capsaicin stimulate the release of inflammatory cytokines in a human bronchial epithelial cell line. Neuropeptides 33: 447-456.

Veronesi, B.; Oortgiesen, M.; Roy, J.; Carter, J. D.; Simon, S. A.; Gavett, S. H. (2000) Vanilloid (capsaicin) receptors influence inflammatory sensitivity in response to particulate matter. Toxicol. Appl. Pharmacol. 169: 66-76.

Veronesi, B.; De Haar, C.; Roy, J.; Oortgiesen, M. (2002a) Particulate matter inflammation and receptor sensitivity are target cell specific. Inhalation Toxicol. 14: 159-183.

Veronesi, B.; De Haar, C.; Lee, L.; Oortgiesen, M. (2002b) The surface charge of particulate matter related to cytokine release in human bronchial epithelial cells (BEAS-2B). Toxicol. Appl. Pharmacol. 178: 144-154.

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.

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.

Wellenius, G. A.; Saldiva, P. H. N.; Batalha, J. R. F.; Murthy, G. G. K.; Coull, B. A.; Verrier, R. L.; Godleski, J. J. (2002) Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction. Toxicol. Sci. 66: 327-335.

Wesselkamper, S. C.; Prows, D. R.; Biswas, P.; Willeke, K.; Bingham, E.; Leikauf, G. D. (2000) Genetic susceptibility to irritant-induced acute lung injury in mice. Am. J. Physiol. 279: L575-L582.

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.

Zelikoff, J. T.; Chen, L. C.; Cohen, M. D.; Fang, K.; Gordon, T.; Li, Y.; Nadziejko, C.; Schlesinger, R. B. (2003) Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. Inhalation Toxicol. 15: 131-150.

Zhang, 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 ASSOCIATED WITH AMBIENT PARTICULATE MATTER

8.1 INTRODUCTION

Epidemiologic studies linking community ambient PM concentrations to health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD; U.S. Environmental Protection Agency, 1996a). Many of those studies reported that measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations are associated with ambient levels of $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, and/or other indicators of PM exposure. Numerous more recent epidemiologic studies discussed in this chapter have also evaluated ambient PM relationships to morbidity and mortality and, thereby, provide an expanded basis for assessment of health effects associated with exposures to airborne PM at concentrations currently encountered in the United States.

The epidemiology studies assessed here are best considered in combination with information on ambient PM concentrations presented in Chapter 3, studies of human PM exposure (Chapter 5), and PM dosimetry and toxicology (Chapters 6 and 7). The epidemiology studies contribute important information on associations between health effects and exposures of human populations to "real-world" ambient PM and also help to identify susceptible subgroups and associated risk factors. Chapter 9 provides an interpretive synthesis of information drawn from this and other chapters.

This chapter opens with discussion of approaches used for selecting studies, followed by a brief overview of key general features of the several types of epidemiologic studies assessed and discussion of important general methodological issues that need to be considered in their critical assessment. Then, Section 8.2 assesses epidemiologic studies of PM effects on mortality; and Section 8.3 evaluates studies of morbidity as a health endpoint. Section 8.4 provides an interpretive assessment of the overall PM epidemiologic data base reviewed in Sections 8.2 and 8.3 in relation to various key issues. The overall key findings and conclusions for this chapter are then summarized in Section 8.5.

8.1.1 Approaches for Identifying and Assessing Studies

Numerous PM epidemiologic papers have been published since completion of the 1996 PM AQCD, and U.S. EPA (NCEA-RTP) has used a systematic approach to identifying pertinent epidemiologic studies for consideration in this chapter. In general, an ongoing continuous Medline search has been employed in conjunction with other strategies to identify PM literature pertinent to developing criteria for PM NAAQS. The literature search method is similar to those used by others (e.g., Basu and Samet, 1999). A publication base was first established by using Medline and other data bases and a set of key words (particles, air pollution, mortality, morbidity, cause of death, PM, etc.) in a search strategy which was later reexamined and modified to enhance identification of pertinent published papers. Since literature searches encounter not a static but a changing, growing stream of information, searches are not run just for the most recent calendar quarter but are backdated in an attempt to capture references added to that time period since the previous search was conducted. Papers were also added to the publication base by EPA staff (a) through review of advance tables of contents of thirty journals in which relevant papers are published and (b) by requesting scientists known to be active in the field to identify papers recently accepted for publication.

While the above search regime builds a certain degree of redundancy into the system, which ensures good coverage of the relevant literature and lessens the possibility of important papers being missed, additional approaches have augmented traditional search methods. First, at the beginning of the process, a Federal Register Notice was issued, requesting information and published papers from the public at large. Next, non-EPA chapter authors are expert in this field; and, while EPA provides them with the outcomes of searches, the authors are also charged with identifying the literature on their own. Finally, a keystone in the literature identification process is that, at several review stages in the process, both the public and CASAC offer comments which also often identify potentially relevant publications.

The publication of new PM studies has been and is proceeding at a prodigious rate; and the acquisition and evaluation of pertinent literature in this PM AQCD development process is an ongoing process which continues to identify new information for consideration. Efforts have been made to assess here pertinent new studies accepted for publication through April, 2002, as well as some published since then (if such recent new papers provide particularly important information helpful in addressing key scientific issues).

Those epidemiologic studies that relate measures of ambient air PM to human health outcomes are assessed in this chapter, whereas studies of (typically much higher) occupational exposures are not considered here. Criteria used for selecting literature for the present assessment include mainly whether a given study includes information on: (1) ambient PM indices (e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, etc.) as a key element; (2) analyses of health effects of specific PM chemical or physical constituents (e.g., metals, sulfates, nitrates or ultrafine particles, etc.); (3) evaluation of health endpoints and populations not previously extensively researched; (4) multiple pollutant analyses; and/or (5) for long-term effects, mortality displacement information.

To produce a thorough appraisal of the evidence, the authors first concisely highlight key points derived from the 1996 PM AQCD assessment of the available information. Then, key new information is presented in succinct text summary tables for important new studies that have become available since the prior PM AQCD. More detailed information on methodological features and results for these and other numerous newly available studies is summarized in tabular form in Appendices 8A and 8B. These appendix tables are generally organized to include: (1) information about study location and ambient PM levels; (2) description of study methods employed; (3) results and comments; and (4) quantitative outcomes for PM measures. In the main body of the chapter, greater emphasis is placed on integrating and interpreting findings from the array of evidence provided by the more important newer studies than on detailed evaluation of each of the numerous newly available studies.

Particular emphasis is focused in the text on those studies and analyses thought to provide information most directly applicable for U.S. standard setting purposes. Specifically, North American studies conducted in the U.S. or Canada are generally accorded more text discussion than those from other geographic regions; and analyses using gravimetric (mass) measurements are generally accorded more text attention than those using non-gravimetric ambient PM measures, e.g., black smoke (BS) or coefficient of haze (CoH). In addition, emphasis is placed on text discussion of (a) new multi-city studies that employ standardized methodological analyses for evaluating PM effects across several or numerous cities and often provide overall effects estimates based on combined analyses of information pooled across multiple cities and/or (b) other studies providing quantitative PM effect-size estimates for populations of interest.

While efforts have been made to acquire and evaluate all pertinent newly available published studies presenting acceptable statistical analysis of health outcomes in relation to quantitative gravimetric measures of exposure to $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, etc., this does not necessarily ensure that all possible studies have been found and summarized in appendix tables or assessed in the main text. Nevertheless, the large database considered, containing such numerous studies, tends to insulate the integration of the body of evidence from the potential impacts of omitting one or another study that may not necessarily be key in and of itself. The interpretation and integration presented are done with the goal of producing an objective appraisal of the evidence, including weighing of alternative views on controversial issues.

In assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in the interpretations of their findings, the following types of questions were considered, as was done in the 1996 PM AQCD:

(1) Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?

(2) Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3) Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4) Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

(5) Were likely important confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

(6) Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

These guidelines provide benchmarks for judging the relative quality of various studies and for selecting the best for use in criteria development. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is

beyond the scope of this document. Of most importance for present purposes are those studies which provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

8.1.2 Types of Epidemiologic Studies Reviewed

Definitions of various types of epidemiologic studies assessed here were provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are briefly summarized here. Briefly, the epidemiologic studies are divided into *mortality* studies and *morbidity* studies. *Mortality* studies evaluating PM effects on total (non-accidental) mortality and cause-specific mortality provide the most unambiguous evidence related to a clearly adverse endpoint. The *morbidity* studies further evaluate PM effects on a wide range of health endpoints, such as cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory symptoms, self-medication in asthmatics, changes in pulmonary function tests (PFT), low birthweight infants, etc.

The epidemiologic strategies most commonly used in PM health studies are of four types: (1) *ecologic studies;* (2) *time-series semi-ecologic studies;* (3) *longitudinal panel and prospective cohort studies;* and (4) *case-control and crossover studies*. In addition, time-series analyses or other analytic approaches have been used in intervention studies. All of these are observational studies rather than experimental studies. In general, the exposure of the participant is not directly observed; and the concentration of airborne particles and other air pollutants at one or more stationary air monitors is used as a proxy for individual exposure to ambient air pollution.

In *ecologic studies*, the responses are at a community level (for example, annual mortality rates), as are the exposure indices (for example, annual average PM concentrations) and covariates (for example, the percentage of the population greater than 65 years of age). No individual data are used in the analysis; therefore, the relationship between health effect and exposure calculated across different communities may not reflect individual-level associations between health outcome and exposure. The use of proxy measures for individual exposure and covariates or effect modifiers may also bias the results, and within-city or within-unit confounding may be overlooked.

Time-series studies are more informative because they allow the study of associations between *changes* in a health outcome and *changes* in exposure indicators preceding or simultaneous with the outcome. The temporal relationship supports a conclusion of a causal relation, even when both the outcome (for example, the number of non-accidental deaths in a city during a day) and the exposure (for example, daily air pollution concentration) are community indices.

Prospective cohort (or panel) studies use data from individuals, including health status (where available), individual exposure (not usually available), and individual covariates or risk factors, observed over time. The participants in a prospective cohort study are ideally recruited (using a simple or stratified random sample) so as to represent a target population for which individual or community exposure of the participants is known before and during the interval up to the time the health endpoint occurs. The use of individual-level data is believed to give prospective cohort studies greater inferential strength than other epidemiologic strategies. The use of community-level or estimated exposure data, if necessary, may weaken this advantage, as it does in time-series studies.

Case-control studies are retrospective studies in that exposure is determined after the health endpoint occurs (as is common in occupational health studies). As Rothman and Greenland (1998) describe it, "Case-control studies are best understood by defining a source population, which represents a hypothetical study population in which a cohort study might have been conducted . . . In a case-control study, the cases are identified and their exposure status is determined just as in a cohort study . . . [and] a control group of study subjects is sampled from the entire source population that gives rise to the cases . . . the cardinal requirement of control selection is that the controls must be sampled independently of their exposure status."

The *case-crossover design* is suited to the study of a transient effect of an intermittent exposure on the subsequent risk of an acute-onset health effect hypothesized to occur a short time after exposure. In the original development of the method, effect estimates were based on within-subject comparisons of exposures associated with incident disease events with exposures at times before the occurrence of disease, using matched case-control methods or methods for stratified follow-up studies with spare data within each stratum. The principle of the analysis is that the exposures of cases just before the event are compared with the distribution of exposure estimated from some separate time period. This distribution is assumed to be representative of

the distribution of exposures for those individuals while they were at risk of developing the outcome of interest.

When measurements of exposure or potential effect modifiers are available on an individual level, it is possible to incorporate this information into a case-crossover study (unlike a time-series analysis). A disadvantage of the case-crossover design, however, is the potential for bias due to time trends in the exposure time-series. Because case-crossover comparisons are made between different points in time, the case-crossover analysis implicitly depends on an assumption that the exposure distribution is stable over time (stationary). If the exposure time-series is non-stationary and case exposures are compared with referent exposures systematically selected from a different period in time, a bias may be introduced into estimates of the measure of association for the exposure and disease. These biases are particularly important when examining the small associations that appear to exist between PM and health outcomes.

Intervention studies (often involving features of time-series or other above types of analyses) provide a particularly powerful additional approach for evaluating possible causal relationships between ambient air pollution variables (e.g., PM) and health effects in human populations. In such studies, the effects of active interventions that result in reductions of one or another or several air pollutants (constituting essentially a "natural experiment") are evaluated in relation to changes in mortality or morbidity outcomes among population groups affected by the reduction in air pollution exposure. To date, only a few epidemiological studies have evaluated the consequences of interventions which allow for comparison of PM-health outcome relationships before and after certain relatively discrete events resulting in notable changes in ambient PM concentrations. Given that etiology of health outcomes related to PM or other air pollutants are typically also affected by other risk factors, it is important in intervention studies not only to measure air pollution exposure and health status before and after air pollution reductions but also to identify and evaluate potential effects of other risk factors before and after air pollution reductions.

The proposition that intervention studies can provide strong support for causal inferences was emphasized by Hill (1965). In his classic monograph (The Environment and Disease: Association or Causation?), Hill (1965) addressed the topic of preventive action and its consequences under Aspect 8, stating:

"Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed."

8.1.3 Confounding and Effect Modification

A pervasive problem in the analysis of epidemiologic data, no matter what design or strategy, is the unique attribution of the health outcome to the nominal causal agent (i.e., airborne particles in this document). The health outcomes attributed to particles are not specific (for example, mortality in a broad range of [International Classification of Disease] ICD-9 categories); and, as such, they may also be attributable to high or low temperatures, influenza and other diseases, and/or exposure to other air pollutants. Many of the other factors can be measured directly or by proxies. Some of these co-variables may be *confounders* and others *effect modifiers*. The distinctions are important.

Confounding is " . . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)." (Rothman and Greenland, 1998, p. 120). These authors list three criteria for a confounding factor:

(1) A confounding factor must be a risk factor for the disease (health effect).

(2) A confounding factor must be associated with the exposure under study in the source population (the population at risk from which the cases are derived).

(3) A confounding factor must not be affected by the exposure or the disease (i.e., it cannot be an intermediate step in the causal path between the exposure and the disease).

Thus, the possible confounder should both be a risk indicator by itself and also be associated with the exposure of interest in the study.

Causal events occur prior to some initial bodily response. A causal association may usually be defined as an association in which alteration in the frequency or quality of one category is followed by a change in the other. The concept of the chain mechanism is that many variables may be related to a single effect through a direct-indirect mechanism. In fact, events are not dependent on single causes. A given chain of causation may represent only a fraction of

a web (MacMahon and Pugh, 1970). A causal pathway refers to the network of relationships among factors in one or more causal chains in which the members of the population are exposed to causal agents that produce the observed health effect. The primary cause may be mediated by secondary causes (possibly proximal to exposure) and may have either a direct effect on exposure or an indirect effect through the secondary causes, or both, as illustrated below. A non-causal pathway may involve factors that are not associated with the health effect or for which there is no population exposure, so that the factors are not potential confounders.

The determination of whether a potential confounder is an actual confounder may be elucidated from biological or physical knowledge about its exposure and health effects. Patterns of association in epidemiology may be helpful in suggesting where to look for this knowledge, but do not replace it. Gaseous criteria pollutants (CO, NO_2, SO_2, O_3) are candidates for confounders because all of these have at least some adverse health effects also associated with particles (CO more often being associated with cardiovascular effects and the others with respiratory effects, including symptoms and hospital admissions). In addition, the gaseous criteria pollutants may be associated with particles for several reasons, including common sources and correlated changes in response to wind and weather. Lastly, SO_2 and NO_2 may be precursors to sulfate and nitrate components of ambient particle mixes, while NO_2 contributes also to the formation of organic aerosols during photochemical transformations.

The problem of disentangling the effects of other pollutants is especially difficult when high correlation exists between one or more of them and ambient PM measurements. A common source, such as combustion of gasoline in motor vehicles emitting CO, NO_2, and primary particles (and often resulting in high correlations), may play an important role in confounding among these pollutants, as do weather and seasonal effects. Even though O_3 is a secondary pollutant also associated with emission of NO_2, it is often more variably correlated with ambient PM concentrations, depending on location, season, etc. Levels of SO_2 in the western U.S. are often quite low, so that secondary formation of particle sulfates plays a much smaller role there, resulting in usually relatively little confounding of SO_2 with PM mass concentration in the West. On the other hand, in the industrial Midwest and northeastern states, SO_2 and sulfate levels during many of the epidemiology studies were relatively high and highly correlated with fine particle mass concentrations, such that criterion 3 (no causal path leading from confounder to exposure, or exposure to confounder to health effect) may not be strictly true

for SO_2 versus sulfate or overall fine particle mass. If the correlation with PM and SO_2 is not too high, it may be possible to estimate some part of their independent effects which depend on the assumption of independence under the particular model analyzed. If there is a causal pathway, then it may be difficult to determine whether the observed relationship of exposure to health effect is a direct effect of the exposure (to sulfate or fine PM in the example), an indirect effect mediated by the potential confounder (i.e., exposure to SO_2), or a mixture of these. Consideration of additional (e.g., exposure, dosimetric, toxicologic) information beyond narrow reliance on observed correlations among the PM measure(s), other pollutants, and health outcome indicators is often useful in helping to elucidate the plausibility of PM or other pollutants being causally related to statistically-associated health effects. As an example, of much relevance is the extent to which the population in a community time-series study or the participants in a prospective cohort study are exposed to measurable levels of the potential confounder, particularly the ambient gaseous co-pollutants. If there is little or no exposure, then the potential confounder does not satisfy the requirement that it is related to both exposure and outcomes. This is discussed in Section 8.4 in connection with the role of exposure measurement errors in air pollution epidemiology.

Some extraneous variables fall into the category of *effect modifiers*. "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification." (Rothman and Greenland, 1998, p. 254). Examples of effect modifiers in some of the studies evaluated in this chapter include environmental variables (such as temperature or humidity in time-series studies), individual risk factors (such as education, cigarette smoking status, age in a prospective cohort study), and community factors (such as percent of population > 65 years old). It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables.

Effect modifiers may be encountered (a) within single-city time-series studies or (b) across cities in a two-stage hierarchical model or meta-analysis. Figure 8-1 illustrates some possibilities, using hypothetical examples with four cities in which a co-pollutant of the PM index is to be evaluated as a possible effect modifier. In the examples in Figure 8-1, the

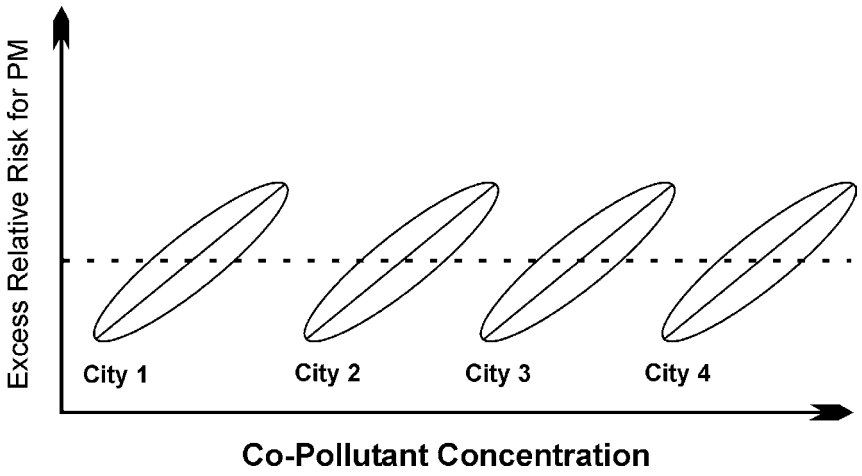

Figure 8-1a. Strong within-city association between PM and mortality, but no second-stage association.

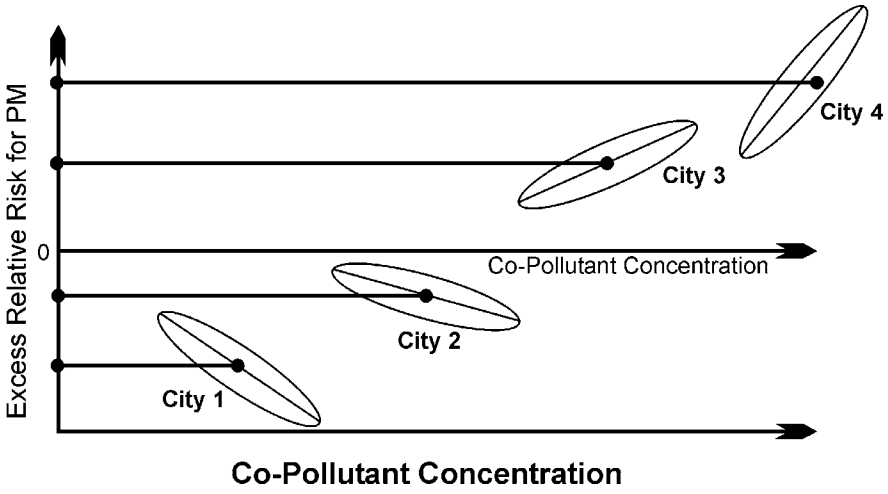

Figure 8-1b. Within-city association between PM and mortality ranges from negative to positive with mean across cities approximately zero, but with strong positive second-stage association.

co-pollutant is assumed to have a relatively high positive correlation with the PM index. It is also assumed that the excess relative risk for PM is calculated in a model in which PM is the only air pollutant. For any given co-pollutant concentration within each city, there is likely to be only a modest range of values of the PM index and the associated excess relative risk, as

suggested by the ellipses in Figure 8-1. The relationship between mortality and PM in Figure 8-1a is assumed to be the same and positive in all four cities; thus, with increasing co-pollutant concentration within each city, the excess relative risk increases because the co-pollutant is strongly correlated with the PM index. However, in the hypothetical 8-1a, the co-pollutant is not an effect modifier for PM, as can be shown by a regression of the estimated mean PM effect on the mean co-pollutant concentration across the four cities.

In Figure 8-1b, the relationship between PM and mortality is assumed to differ across the four cities, ranging from strongly negative in City 1 to strongly positive in City 4. Thus, with increasing co-pollutant concentration within each city, the excess relative risk decreases in City 1 and City 2 (but increases in City 3 and City 4) because the co-pollutant is strongly correlated with the PM index. In Figure 8-1b, the co-pollutant is a hypothetical effect modifier for PM, as can be shown by a regression of the estimated mean PM effect on the mean co-pollutant concentration across the four cities, even though the simple mean of the excess relative risks across the four cities is nearly zero. A relationship would be found if all within-city effects were positive or if the across-city ecological regression were negative. Stratification by levels of the putative effect modifier is also often useful.

Potential confounding (Figure 8-2a) is more difficult to identify and several statistical methods are available, none of them being completely satisfactory. The usual methods include the following:

Within a city:

(A) Fit both a single-pollutant model and then several multi-pollutants models, and determine if including the co-pollutants greatly changes the estimated effect and inflates its estimated standard error;

(B) If the PM index and its co-pollutants are nearly multi-collinear, carry out a factor analysis, and determine which gaseous pollutants are most closely associated with PM in one or more common factors;

Using data from several cities:

(C) Proceed as in Method A and pool the effect size estimates across cities for single- and multi-pollutant models;

(D) Carry out a hierarchical regression of the PM effects versus the mean co-pollutant concentration and determine if there is a relationship; and

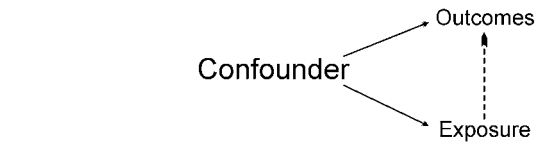

Figure 8-2a

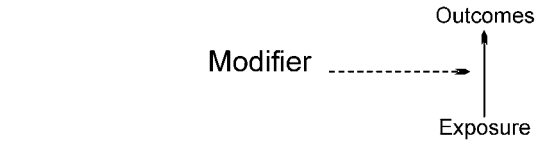

Figure 8-2b

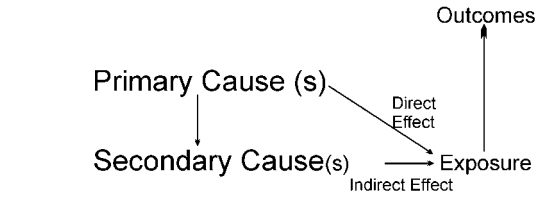

Figure 8-2c

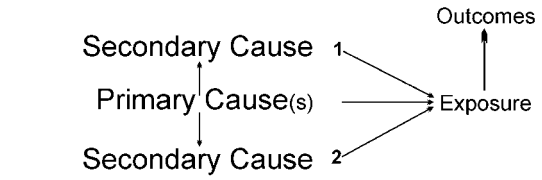

Figure 8-2d

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.

(E) First carry out a regression of PM versus the co-pollutant concentration within each city and the regression coefficient of mortality versus PM for each city. Then fit a second-stage model regressing the mortality-PM coefficient versus the PM-co-pollutant coefficient, concluding that the co-pollutant is a confounder if there is an association at the second stage (See Figure 8-2c).

Each of the above methods (A through E) are subject to one or more disadvantages. The multi-pollutant regression coefficients in method A, for example, may be unstable and have

greatly inflated standard errors, weakening their interpretation. In method B, the factors may be sensitive to the choice of co-pollutants and the analysis method, and may be difficult to relate to real-world entities. In method C, as with any meta-analysis, it is necessary to consider the heterogeneity of the within-city effects before pooling them. Some large multi-city studies have revealed unexpected heterogeneity, not fully explained at present. While method D is sometimes interpreted as showing confounding if the regression coefficient is non-zero, this is an argument for effect modification, not confounding. Method E is sensitive to the assumptions being made; for instance, if PM is the primary cause in Figure 8-2c and the co-pollutant the secondary cause, then the two-stage approach may be valid. However, if the model is mis-specified and there are two or more secondary causes, some of which may not be identified, then the method may give misleading results.

Given the wide array of considerations and possibilities discussed above, it is extremely important to recognize that there is no single "correct" approach to modeling ambient PM-health effects associations that will thereby provide the "right" answer with regard to precise quantification of PM effect sizes for different health outcomes. Rather, it is clear that emphasis needs to be placed here on (a) looking for convergence of evidence derived from various acceptable analyses of PM effects on a particular type of health endpoint (e.g., total mortality, respiratory hospital admissions, etc.); (b) according more weight to those well-conducted analyses having greater power to detect effects and yielding narrower confidence intervals; and (c) evaluating the coherence of findings across pertinent health endpoints and effect sizes for different health outcomes. With regard to the latter, for example, the credibility of the overall array of epidemiologically-demonstrated health effects being causally related to ambient PM exposure is greatly enhanced to the extent that effect sizes for hospital admissions are larger than those for PM-mortality effects and those for physician and emergency department visits are at least as large as those for hospital admissions, and so on for respiratory symptoms, asthma medication use, etc.

The issue of what PM effect sizes should be the main focus of presentation and discussion in ensuing text – i.e., those derived from single-pollutant models including only PM or effect sizes derived from multi-pollutant models that include one or more other copollutants along with the PM indicator(s) – is an important one. Again, there is not necessarily any single "correct" answer on this point. Implicit in arguments asserting that multi-pollutant model results must be

reported and accorded equal or more weight than single-pollutant model PM results is a functional construct that has generally been used in epidemiologic modeling of health effects of air pollution, a functional construct that considers the various air pollutants mainly independently of one another in terms of their health effects, which may not necessarily be the case. This may be causing either over- or under-estimation of PM health effects, depending on the modeling choices made by the investigator and the study situation. For example, ozone and $PM_{2.5}$ can share some similar oxidative formation and effect pathways in exerting adverse health effects on the lung, yet are often modeled as independent pollutants or are placed in models simultaneously, even though they may have high correlations over space and time and in their health effects on the human body. Another complication is that other pollutants can be derived from like sources and may serve less as a measure of direct effects than as a marker of pollution from a specific source. As an example noted earlier, SO_2 and $PM_{2.5}$ are often predominantly derived from the same sources in a locale (e.g., coal-fired power plants in the mid-western U.S.), so that putting these two pollutants in a model simultaneously may cause a diminution of the $PM_{2.5}$ coefficient that may be misleading.

One approach that has been taken is to look at pollutant interactions (either multiplicative or additive, depending on the model assumed), but until we understand (and appropriately model) the biological mechanisms, such models are assumptions on the part of the researcher. Present modeling practices represent the best methods now available and provide useful assessments of PM health effects. However, ultimately, more biological-plausibility based models are needed that more accurately model pollutant interactions and allow more biologically-based interpretations of modeling results, rather than simply relying on a statistical model specification or specific modeling criteria to determine the "winner" co-pollutant.

Until more is known about multiple pollutant interactions, it is important to avoid over-interpreting model results regarding the relative sizes and significance of specific pollutant effects, but instead to use biological plausibility in interpreting model results. For example, as discussed later, Krewski et al (2000) found significant associations for both PM and SO_2 in their reanalysis for the Health Effects Institute of the ACS data set published by Pope et al. (1995). Regarding these pollutant associations, they concluded that: "The absence of a plausible toxicological mechanism by which sulfur dioxide could lead to increased mortality further suggests that it might be acting as a marker for other mortality-associated pollutants." (Note:

Annual mean SO_2 averaged < 10 ppb across ca. 125 cities in ACS data set.) Rather than letting statistical significance be the sole determinant of the "most important" pollutant, the authors utilized biological plausibility to conclude which association was most likely driving the pollution-health effects association in question. In the future, such biological plausibility/mechanistic considerations need to be similarly considered in modeling and weighing pollutant interactions in evaluating the health effects of PM. In the meantime, the results from single-pollutant models of PM effects are emphasized here, as being those most likely reflecting overall effects exerted by ambient PM either acting alone and/or in combination with other ambient air pollutants.

8.1.4 GAM Convergence Issue

In the spring of 2002, the original investigators of a key newly available multi-city study (the National Mortality and Morbidity Air Pollution Study; NMMAPS) cosponsored by the Health Effects Institute (HEI) reported that use of the default convergence criteria setting used in the GAM routine of certain widely-used statistical software (Splus) could result in biased estimates of air pollution effects when at least two non-parametric smoothers are included in the model (Health Effects Institute letter, May 2002). The NMMAPS investigators also reported (Dominici et al., 2002), as determined through simulation, that such bias was larger when the size of risk estimate was smaller and when the correlation between the PM and the covariates (i.e., smooth terms for temporal trend and weather) was higher. While the NMMAPS investigators reported that reanalysis of the 90 cities air pollution-mortality data (using stringent convergence criteria) did not qualitatively change their original findings (i.e., the positive association between PM_{10} and mortality; lack of confounding by gaseous pollutants; regional heterogeneity of PM, etc.), the reduction in the PM_{10} risk estimate was apparently not negligible (dropping, upon reanalysis, from 2.1% to 1.4% excess deaths per 50 $\mu g/m^3$ increase in PM_{10}).

Issues surrounding potential bias in PM risk estimates from time-series studies using GAM analyses and default convergence criteria were raised by EPA and discussed in July 2002 at the CASAC review of the Third External Review Draft of this PM AQCD. In keeping with a follow up consultation with CASAC in August 2002, EPA encouraged investigators for a number of important published studies to reanalyze their data by using GAM with more stringent convergence criteria, as well as by using Generalized Linear Model (GLM) analyses with

parametric smoothers that approximated the original GAM model. EPA, working closely with HEI, also arranged for (a) the resulting reanalyses first to be discussed at an EPA-sponsored open Workshop on GAM-Related Statistical Issues in PM Epidemiology held in November 2002; (b) then for any revamping of the preliminary analyses in light of the workshop discussions; before (c) submittal by the investigators of short communications describing the reanalyses approaches and results to EPA and HEI for peer-review by a special panel assembled by HEI; and (d) the publication of the short communications on the reanalyses, along with commentary by the HEI peer-review panel, in an HEI Special Report (2003a). Some of the short-communications included in the HEI Special Report (2003a) included discussion of reanalyses of data from more than one original publication because the same data were used to examine different issues of PM-mortality associations (e.g., concentration/response function, harvesting, etc.). In total, reanalyses were reported for more than 35 originally published studies.

8.1.5 Ambient PM Increments Used to Report Risk Estimates

The effect of mortality from exposure to PM or other pollutants is usually expressed in this document 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. As reported in Samet et al. (2000a), there was little association between PM_{10} effect size and crude mortality rate in the continental U.S. cities.

The PM increments used in this document to convert regression coefficients into meaningful increments of excess risk are based on data from the U.S. fine particle monitoring network for 1999 and 2001, the most recent years available. The difference between the annual mean and the annual 95th percentile was used to characterize annual variation within each site; and the average across all sites was used to select an appropriate increment for short-term studies, about 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$, after rounding for ease of calculation. The difference between the average of annual mean PM concentrations across all sites and the average of the annual 95th percentiles across all sites was about 20 $\mu g/m^3$ for PM_{10} and 10 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$, values used here for PM increments in long-term studies.

Thus, the pollutant concentration increments utilized here to report Relative Risks (RR's) or Odds Ratio for various health effects are as follow for short-term (≤ 24 h) exposure studies: 50 μg/m^3 for PM_{10}; 25 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$; 155 nmoles/m^3 (15 μg/m^3) for SO_4^{-2}; and 75 nmoles/m^3 (3.6 μg/m^3, if as H_2SO_4) for H^+. The increments for short-term studies are the same as were used in the 1996 PM AQCD, a choice now driven by more current data. In the 1996 PM AQCD, the same increments were used for the long- and short-term exposure studies. However, for long-term exposure studies, 20 μg/m^3 is the increment used here for PM_{10} and 10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$ for long-term exposure studies. These latter increments, derived from new 1999-2001 data, are smaller than those used in the 1996 PM AQCD for long-term studies.

8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE

8.2.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been studied extensively and represents an important issue addressed in previous PM criteria assessments (U.S. Environmental Protection Agency, 1986, 1996a). Recent findings are evaluated here mainly for the two most important epidemiology designs by which mortality is studied: time-series mortality studies (Section 8.2.2) and prospective cohort studies (Section 8.2.3). The time-series studies mostly assess acute responses to short-term PM exposure, although some recent work suggests that time-series data sets can also be useful in evaluating responses to exposures over a longer time scale. Time-series studies use community-level air pollution measurements to index exposure and community-level response (i.e., the total number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully complement time-series studies; they typically evaluate human health effects of long-term PM exposures indexed by community-level measurements, using individual health records with survival lifetimes or hazard rates adjusted for individual risk factors.

8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

The time-series mortality studies reviewed in the 1996 and other past PM AQCD's provided much evidence that ambient PM air pollution is associated with increases in daily mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published between 1988 and 1996. Of these studies, only five studies used GAM with default convergence criteria. Recent reanalyses (Schwartz, 2003a; Klemm and Mason, 2003) using GAM with stringent convergence criteria and other non-GAM approaches for one of these five studies, i.e., the Harvard Six cities time-series analysis (the only multi-city study among the five studies), essentially confirmed the original findings. Thus, information provided in the 1996 PM AQCD can be summarized without major concern with regard to the GAM convergence issue. Information derived from those studies was generally consistent with the hypothesis that PM is a causal agent in contributing to short-term air pollution exposure effects on mortality.

The PM_{10} relative risk estimates derived from short-term PM_{10} exposure studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is most clearly associated with an increased risk of premature total non-accidental mortality (total deaths minus those from accident/injury) on the order of relative risk (RR) = 1.025 to 1.05 in the general population or, in other words, 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increase. Higher relative risks were indicated for the elderly and for those with pre-existing cardiopulmonary conditions. Also, based on the Schwartz et al. (1996a) analysis of Harvard Six City data (as later confirmed in the reanalysis by Schwartz [2003a] and Klemm and Mason [2003]), the 1996 PM AQCD found the RR (combined across the six cities) for excess total mortality in relation to 24-h fine particle concentrations to be about 3% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$ increment.

While numerous studies reported PM-mortality associations, important issues needed to be addressed in interpreting their findings. The 1996 PM AQCD evaluated in considerable detail several critical issues, including: (1) seasonal confounding and effect modification; (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold; (6) harvesting and life shortening; and (7) the role of PM components. As important issues related to model specification became further clarified, more studies began to address the most critical issues, some of which were at least partially resolved, whereas others

required still further investigation. The next several paragraphs summarize the status of these issues at the time of the 1996 PM AQCD publication.

One of the most important components in time-series model specification is adjustment for seasonal cycles and other longer-term temporal trends. Residual over-dispersion and autocorrelation result from inadequate control for these temporal trends, and not adequately adjusting for them could result in biased RRs. Modern smoothing methods allow efficient fits of temporal trends and reduce such statistical problems (it did introduce additional issues as discussed in later sections). Most recent studies controlled for seasonal and other temporal trends, and it was considered unlikely that inadequate control for such trends seriously biased estimated PM coefficients. Effect modification by season was examined in several studies. Season-specific analyses are often not feasible in small-sized studies (due to marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season. It was not fully resolved, however, whether these results represent real seasonal effect modifications or are due to varying extent of correlation between PM and co-pollutants or weather variables by season.

While most available studies included control for weather variables, some reported sensitivity of PM coefficients to weather model specification, leading some investigators to speculate that inadequate weather model specifications may still have erroneously ascribed residual weather effects to PM. Two PM studies (Samet et al., 1996; Pope and Kalkstein, 1996) involved collaboration with a meteorologist and utilized more elaborate weather modeling, e.g., use of synoptic weather categories. Both of these studies used GAM, presumably with default convergence criteria, and therefore need to be interpreted with caution. However, these studies found that estimated PM effects were essentially unaffected by the synoptic weather variables and also indicated that the synoptic weather model did not provide better model fits in predicting mortality when compared to other weather model specifications used in previous PM-mortality studies. Thus, these results suggested that the reported PM effects were not explained by more sophisticated synoptic weather models.

Many earlier PM studies considered at least one co-pollutant in the mortality regression, and some also examined several co-pollutants. In most cases, when PM indices were significant in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate the PM associations. When multiple pollutant models were performed by

season, the PM coefficients became less stable, again, possibly due to PM's varying correlation with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM indices showed the highest significance (versus gaseous co-pollutants) in single and multiple pollutant models. Thus, it was concluded that PM-mortality associations were not seriously distorted by co-pollutants, but interpretation of the relative significance of each pollutant in mortality regression as relative causal strength was difficult because of limited quantitative information on relative exposure measurement/characterization errors among air pollutants.

Measurement error can influence the size and significance of air pollution coefficients in time-series regression analyses and is also important in assessing confounding among multiple pollutants, as varying the extent of such error among the pollutants could also influence the corresponding relative significance. The 1996 PM AQCD discussed several types of such exposure measurement or characterization errors, including site-to-site variability and site-to-person variability — errors thought to bias the estimated PM coefficients downward in most cases. However, there was not sufficient quantitative information available to estimate such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Several studies indicated that associations were seen monotonically below the existing PM standards. It was considered difficult, however, to statistically identify a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models was considered adequate and appropriate.

The extent of prematurity of death (i.e., mortality displacement or "harvesting") in observed PM-mortality associations has important public-health-policy implications. At the time of the1996 PM AQCD review, only a few studies had investigated this issue. While one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalizable because this estimate was obtained for identifiable PM episodes. There was not sufficient evidence to suggest the extent of prematurity for non-episodic periods from which most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

> In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence

> prevent quantification of years of life lost to such mortality in the population. Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized. (p. 13-45)

Only a limited number of PM-mortality studies analyzed fine particles and chemically specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15\text{-}2.5}$) and PM chemical components (sulfates and H^+). The results suggested that, among the components of PM, $PM_{2.5}$ was most significantly associated with mortality. Because the original study was conducted using GAM with default convergence criteria, the data were recently reanalyzed by Schwartz (2003a), who reanalyzed only $PM_{2.5}$ and by Klemm and Mason (2003), who analyzed $PM_{2.5}$, $PM_{10/15}$, $PM_{10/15\text{-}2.5}$, and sulfate. Although the excess risk estimates were somewhat lower than those in the original study, Klemm and Mason's reanalysis confirmed the original findings with regard to the relative importance of fine versus coarse particles. While H^+ was not significantly associated with mortality in the original and an earlier analysis (Dockery et al., 1992), the smaller sample size for H^+ than for other PM components made a direct comparison difficult. The 1996 PM AQCD also noted that mortality associations with BS or CoH reported in earlier studies in Europe and the U.S. during the 1950s to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50% cut-points ($\leq$ 4.5 μm). Furthermore, certain respiratory morbidity studies showed associations between hospital admissions/visits with components of PM in the fine particle range. Thus, the U.S. EPA 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Overall, then, the status of key issues raised in the 1996 PM AQCD can be summarized as follows: (1) the observed PM effects are unlikely to be seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) the observed PM effects are unlikely to be seriously confounded by weather (at least by synoptic weather models); (3) the observed PM effects may be to some extent confounded or modified by co-pollutants, and such extent may vary from season to season; (4) determining the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement characterization error among pollutants (there was not sufficient information on this); (5) no clear evidence for any threshold

for PM-mortality associations was reported (statistically identifying a threshold from existing data was also considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was conducted to investigate harvesting in non-episodic U.S. data); (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in the light of historical data, biological plausibility, and the results from morbidity studies, a greater role for fine particles than coarse particles was suggested in the 1996 PM AQCD as being likely. The AQCD concluded:

> The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, mis-specification of concentration-effect models, biases in study design or implementation, measurement of errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiologic studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS. (p. 13-92)

8.2.2.2 Newly Available Information on Short-Term Mortality Effects

Since the 1996 PM AQCD, numerous new studies have examined short-term associations between PM indices and mortality. Of these studies (over 80 studies), nearly 70% used GAM (presumably with default convergence criteria). In the summer of 2002, U.S. EPA asked the original investigators of some of these studies to reanalyze the data using GAM with more stringent convergence criteria and GLM with parametric smoothers such as natural splines. Because the extent of possible bias caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here will focus only on those studies that did not use GAM Poisson models and those studies that have reanalyzed data using more stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and daily mortality that meet these criteria are summarized in Table 8-1. More detailed summaries of all the short-term exposure PM-mortality studies, including other geographic areas (e.g., Europe, Asia, etc) are described in

TABLE 8-1. RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	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); Dominici et al. (2003)	A	88 cities in the 48 contiguous U.S. states plus AK and HI, 1987-1994; mainly 20 largest.	PM_{10}, O_3, CO, NO_2, SO_2	Numerous models; range of PM_{10} values depending on city, region, co- pollutants. Pooled estimates for 88 cities, individual estimates for 20 largest with co- pollutant models.
Daniels et al. (2000); Dominici et al. (2003)	A	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) Dominici et al. (2003)	A	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, Northeast regions, and overall, but non-linear (usually concave) in the other regions. Possible thresholds in Southeast.
Studies using every day PM_{10} data				
Schwartz (2000a); Schwartz (2003b)	A	Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993.	PM_{10} , O_3, CO, NO_2, SO_2	Pooled PM_{10} (0 and 1 day lag average) mortality estimates for the ten cities were presented. Confounding and/or effect modification was examined for season, co-pollutants, in- versus out-of-hospital deaths.
Schwartz (2000b); Schwartz (2003b).	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Several pooled estimates across cities evaluated for single day, moving average, and distributed lags.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Multi- City Mortality Studies in the U.S. and Canada (cont'd)				
Studies using every day PM_{10} data (cont'd)				
Braga et al. (2001); Schwartz (2003b)	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Pooled estimates across cities evaluated for deaths due to pneumonia, COPD, cardiovascular, and myocardial infarction using distributed lags models.
Moolgavkar (2000a); Moolgavkar (2003).	A	Three large U.S. counties (cities): Cook Co., IL; Los Angeles Co., CA; Maricopa Co., (Phoenix), AZ, 1987-1995 in the original analysis. In the reanalysis, Maricopa Co. was not analyzed.	PM_{10} in all three; $PM_{2.5}$ in Los Angeles. O_3, CO, NO_2, and SO_2 in some models. In the GAM reanalysis, O_3 was not analyzed.	Gaseous pollutants were at least as significantly associated as PM indices. In particular, CO was the best single index of air pollution association with mortality in Los Angeles.
Laden et al.. (2000); Schwartz (2003a)	A	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.
Klemm et al., (2000); Klemm and Mason (2003)	A	Same six cities as (Laden et al., 2000), 1979-1988.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates	Replicated Schwartz et al. (1996a) with additional sensitivity analyses.
Tsai et al. (1999, 2000)	B	Camden, Elizabeth, and Newark, NJ, 1981-1983.	$PM_{2.5}$, PM_{15}, sulfates, trace elements.	Significant effects of $PM_{2.5}$, PM_{10}, and sulfates in Newark, Camden at most lags, but not Elizabeth. Source-specific factors (oil burning, automobiles) were also associated with mortality.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Multi- City Mortality Studies in the U.S. and Canada (cont'd)				
Studies using every day PM_{10} data (cont'd)				
Clyde et al. (2000)	B	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); Burnett and Goldberg (2003)	A	Eight Canadian cities: Montreal, Ottawa, Toronto, Windsor, Calgary, Edmonton, Winnipeg, Vancouver, 1986-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, O_3, CO, NO_2, SO_2.	The results of reanalysis indicate no clear difference in association with mortality between $PM_{2.5}$ and $PM_{10-2.5}$.
Single-City Mortality Studies in the U.S. and Canada				
Ostro et al. (1999a, 2000); Ostro et al. (2003)	A	Coachella Valley (Palm Springs), CA, 1989-1998.	PM_{10} in earlier study, $PM_{2.5}$ and $PM_{10-2.5}$ in later study; O_3, CO, NO_2. Reanalysis reported PM risk estimates only.	PM_{10} (~65% of which was coarse particles) and $PM_{10-2.5}$ (missing values predicted from PM_{10}) were associated with cardiovascular mortality. $PM_{2.5}$ was available for shorter period.
Fairley (1999); Fairley (2003)	A	Santa Clara County (San Jose), CA, 1989-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, O_3, CO, NO_2.	All significant in one- pollutant models, nitrates significant in all multi- pollutant models, $PM_{2.5}$ significant except with particle nitrates.
Schwartz et al. (1999)	B	Spokane, WA, 1989-1995.	PM_{10} only.	No association between mortality and high PM_{10} concentrations on dust storm days with high concentrations of crustal particles.
Lippmann et al. (2000); Ito (2003)	A	Detroit, MI, 1985-1990; 1992-1994 (separate analysis for two periods).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, TSP, O_3, CO, NO_2, SO_2	PM mass indices were more strongly associated mortality than sulfate or acidity. The extent of association with health outcomes was similar for $PM_{2.5}$ and PM_{10-25}.
Chock et al. (2000)	B	Pittsburgh, PA, 1989-1991.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, NO_2, SO_2	Fine and coarse particle data on about 1/3 of days with PM_{10}. Data split into ages < 75 and 75+, and seasons. Significant effects for PM_{10} but not for other size fractions, likely because of smaller sample size.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Klemm and Mason (2000)	B	Atlanta, GA, 1998-1999 (one year).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, oxygenated hydrocarbons (HC), elemental carbon (EC), organic carbon (OC), sulfates, acidity	No significant effects likely due to short time-series (ca. one year).
Schwartz (2000c); Schwartz (2003a)	A	Boston, MA, 1979-1986.	$PM_{2.5}$	Larger effects with longer-term $PM_{2.5}$ and mortality moving averages (span 15 to 60 days) for total and cause-specific mortality.
Lipfert et al. (2000a)	B	Philadelphia, PA- Camden, NJ seven- county area, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, metals, O_3, CO, NO_2, SO_2	Exploration of mortality in different areas relative to air monitor location. Peak O_3 very significant, greatly reduced PM coefficients.
Levy (1998)	B	King County (Seattle), WA, 1990-1994.	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); Mar et a. (2003)	A	Phoenix, AZ, near the EPA platform monitor, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, $PM_{2.5}$ metals, EC, OC, O_3, CO, NO_2, SO_2, and source-apportioned factor scores.	Only cardiovascular mortality was reanalyzed; it was significantly associated with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, factors associated with motor vehicle, vegetative-burning, and regional sulfate.
Clyde et al. (2000)	B	Phoenix, AZ, 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Effect on elderly mortality consistently higher for $PM_{10-2.5}$ among 25 "best" models. Estimates combined using Bayesian model averaging.
Smith et al. (2000)	B	Phoenix, AZ (within city and within county), 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Significant linear relationship with $PM_{10-2.5}$, not $PM_{2.5}$ Piecewise linear models with possible $PM_{10-2.5}$ threshold for elderly mortality 20-25 $\mu g/m^3$.
Gamble (1998)	B	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

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Ostro (1995)	B	San Bernardino and Riverside Counties, CA, 1980- 1986.	$PM_{2.5}$ estimated from visual range, O_3	Positive, significant $PM_{2.5}$ association only in summer.
Murray and Nelson (2000)	B	Philadelphia, PA, 1973- 1990	TSP only	Kalman filtering used to estimate hazard function in a state space model. Both TSP and the product of TSP and average temperature are significant, but not together. Includes estimate of risk population.
Neas et al. (1999)	B	Philadelphia, PA 1973- 1980	TSP only	Case- crossover study. Significant TSP mortality associations reported.
Goldberg et al. (2001a,b,c,d; 2003); Goldberg and Burnett (2003)	A	Montreal, PQ, Canada, 1984- 1995	CoH and extinction were available daily. $PM_{2.5}$ and PM_{10} every sixth day until 1992, daily through 1993.	Reanalysis indicated attenuation of PM risk estimates, especially sensitive to weather model specification. Congestive heart failure, as classified based on medical records from insurance plan, was associated with CoH, SO_2, and NO_2.
Ozkaynak et al. (1996)	B	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 most cause- specific deaths.

*Brief summary of new time-series studies on daily mortality since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1996a). More complete descriptive summaries are provided in Appendix Table 8A-1. The endpoint is total daily non- trauma mortality, unless noted otherwise. Due to the large number of models reported for sensitivity analyses for some of these papers, some evaluating various lags and co-pollutant models, some for individual cities, and others for estimates pooled across cities, quantitative risk estimates are not presented in this table.

**Type: Type of studies: (A) Original study used GAM model including non-parametric smoothing terms with default or other lax convergence criteria, but was reanalyzed using stringent convergence criteria and/or using parametric smoothers; (B) Original study used GLM with parametric smoothers or other approaches, or used GAM but with only one non-parametric smoother.

DRAFT-DO NOT QUOTE OR CITE

Appendix Table 8A-1. These include the studies that apparently used GAM with default convergence criteria, and these studies are noted as such. Information on study location and period, levels of PM, health outcomes, methods, results, and reported risk estimates and lags is provided in Table 8A-1. In addition to these summary tables, discussion in the text below highlights findings from several multi-city studies. Discussion of implications of new study results for types of issues identified in foregoing text is mainly deferred to Section 8.4.

The summary of studies in Table 8-1 and 8A-1 (and in other tables) is not meant to imply that all listed studies should be accorded equal weight in the overall interpretive assessment of evidence regarding PM-associated health effects. In general, for those studies not clearly flawed and having adequate control for confounding increasing scientific weight should be accorded to in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally produce less precise estimates than large studies with an adequate exposure gradient. Therefore, the range of exposures (e.g., as indicated by the IQR), the size of the study as indexed by the total number of observations (e.g., days) and total number of events (i.e., total deaths), and the inverse variance for the principal effect estimate are all important indices useful in determining the likely precision of health effects estimates and in according relative scientific weight to the findings of a given study. As can be seen in Tables 8-1 and 8A-1, nearly all of the newly reported analyses with a few exceptions continue to show statistically significant associations between short-term (24 h) PM exposures indexed by a variety of ambient PM measurements and increases in daily mortality in numerous U.S. and Canadian cities, as well as elsewhere around the world. Also, the effects estimates from the newly reported studies are generally consistent with those derived from the 1996 PM AQCD assessment, the newly reported PM risk estimates generally falling within the range of ca. 1 to 8% increase in excess deaths per 50 $\mu g/m^3$ PM_{10} and ca. 2 to 6% increase per 25 $\mu g/m^3$ $PM_{2.5}$. Several newly available PM epidemiologic studies that conducted time-series analyses in multiple cities are of particular interest, as discussed below. Multi-city studies, such as the NMMAPS study, avoid potential publication bias, because the cities were selected on the basis of population size and the presence of PM monitoring data. In addition, because use of uniform statistical analytical methods, findings cannot be attributed to different analytical approaches.

8.2.2.3 New Multi-City Studies

The new multi-city studies are of particular interest here due to their evaluation of a wide range of PM exposures and large numbers of observations holding promise of providing more precise effects estimates than most smaller scale independent studies of single cities. Another major advantage of the multi-city studies, over meta-analyses for multiple "independent" studies, is the consistency in data handling and model specifications that eliminates variation due to study design. Further, unlike regular meta-analysis, they clearly do not suffer from potential omission of negative studies due to "publication bias." Furthermore, geographic patterns of air pollution effects can be systematically evaluated in multiple-city analyses. Thus, the results from multi-city studies can provide especially valuable evidence regarding the consistency and/or heterogeneity, if any, of PM-health effects relationships across geographic locations. Also, many of the cities included in these multi-city studies were ones for which no time-series analyses had been previously reported. Most of these new multi-city studies used GAM Poisson models, but the data sets have recently been reanalyzed using GAM models with more stringent convergence criteria, as well as by GLM with parametric smoothers.

8.2.2.3.1 U.S. Multi-City Studies

U.S. PM_{10} 90-Cities NMMAPS Analyses

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-series analyses of PM_{10} effects on mortality during 1987-1994 in the 90 largest U.S. cities (Samet et al., 2000a,b), in the 20 largest U.S. cities in more detail (Dominici et al., 2000a), and PM_{10} effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b). These NMMAPS analyses are marked by extremely sophisticated statistical approaches addressing issues of measurement error biases, co-pollutant evaluations, regional spatial correlation, and synthesis of results from multiple cities by hierarchical Bayesian meta-regressions and meta-analyses. These analyses provide extensive new information of much importance and relevance to the setting of U.S. PM standards, because no other study has examined as many U.S. cities in such a consistent manner. That is, NMMAPS used only one consistent PM index (PM_{10}) across all cities (noted PM_{10} samples were only collected every 6 days in most of the 90 cities); death records were collected in a uniform manner; and demographic variables were uniformly addressed. The 90-cities analyses studies employ multi-stage models (see Table 8-1)

in which heterogeneity in individual city's coefficients in the first stage Poisson models were evaluated in the second stage models with city- or region-specific explanatory variables.

As noted earlier, the original investigators of the NMMAPS study reported in 2002 a potential problem with using the GAM Poisson models with default convergence criteria available in popular statistical software in estimating air pollution risks (Dominici et al., 2002). The default convergence criteria were too lax to attain convergence in the setting of air pollution, weather, and mortality/morbidity parameters where "small" PM regression coefficients were estimated and at least two covariates were modeled with non-parametric smoothers. Their simulation analysis also suggested that the extent of bias could be more serious when the magnitude of risk coefficient was smaller and when PM's correlation with covariates was stronger. The investigators since then reanalyzed the 90 cities data, using more stringent convergence criteria as well as using fully parametric smoothers, and reported revised results. The following description of the NMMAPS mortality study therefore focuses on the results of the reanalysis of the 90 cities study.

In the original and reanalyzed 90 cities studies, the combined estimates of PM_{10} coefficients were positively associated with mortality at all the lags examined (0, 1, and 2 day lags), although the 1-day lag PM_{10} resulted in the largest overall combined estimate. Figure 8-3 shows the reanalyzed results for the estimated percent excess total deaths per 10 $\mu g/m^3$ PM_{10} at lag 1 day in the 88 (90 minus Honolulu and Anchorage) largest cities, as well as (weighted average) combined estimates for U.S. geographic regions depicted in Figure 8-4. The majority of the coefficients were positive for the various cities listed along the left axis of Figure 8-3. The estimates for the individual cities were first made separately. The cities were then grouped into the 7 regions seen in Figure 8-4 (based on characteristics of the ambient PM mix typical of each region, as delineated in the 1996 PM AQCD). The bolded segments represent the posterior means and 95% posterior intervals of the pooled regional effects without borrowing information from other regions. The triangle and bolded segment at the bottom of Figure 8-3 display the combined estimate of overall nationwide effects of PM_{10} for all the cities.

Note that there appears to be some regional-specific variation in the overall combined estimates for all the cities in a given region. This can be discerned more readily in Figure 8-5, which depicts overall region-specific excess risk estimates for 0, 1, and 2 day lags. For example, the coefficients for the Northeast are generally higher than for other regions. The NMMAPS

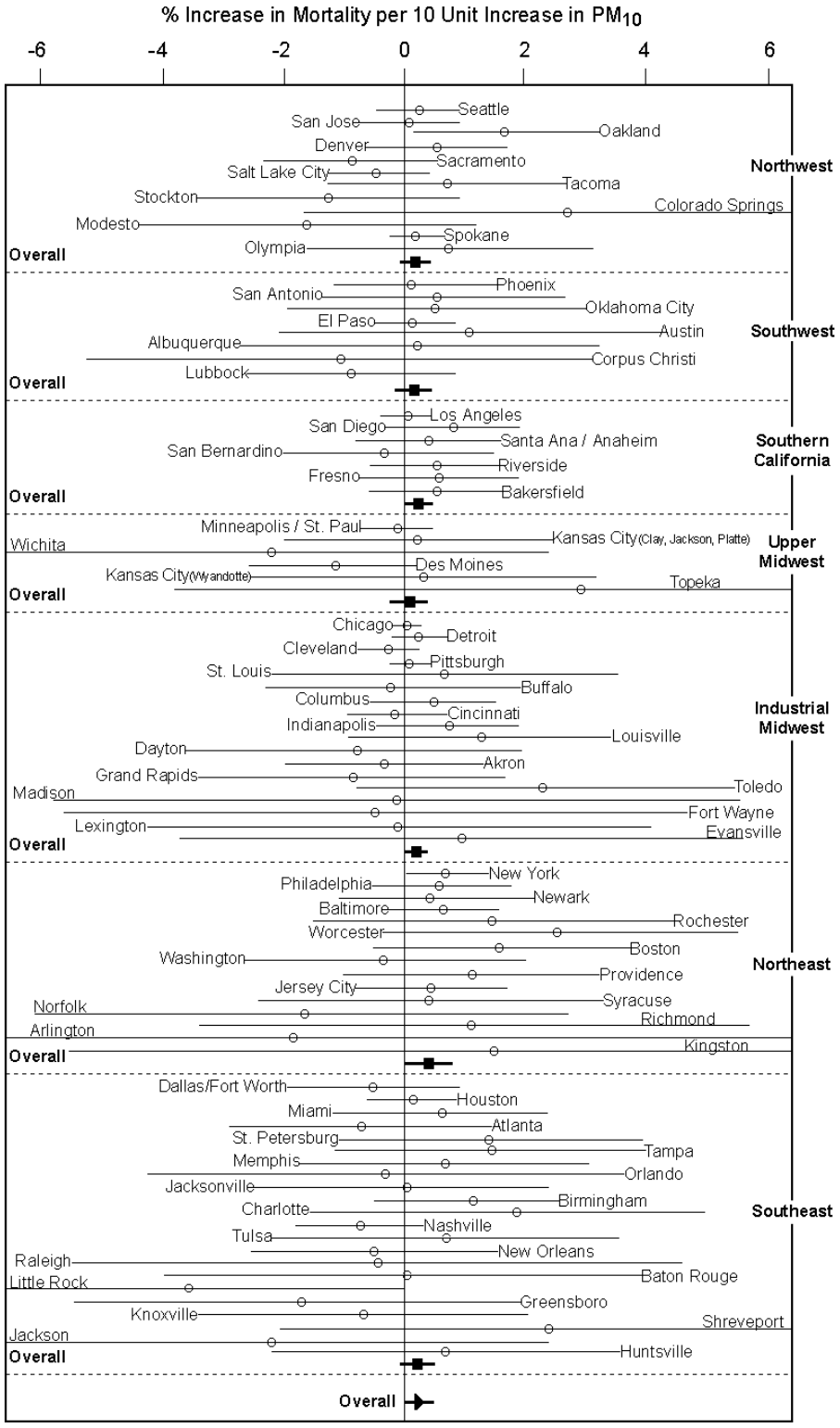

Figure 8-3. Estimated excess risks for PM mortality (1 day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis.

Source: Dominici et al. (2002; 2003).

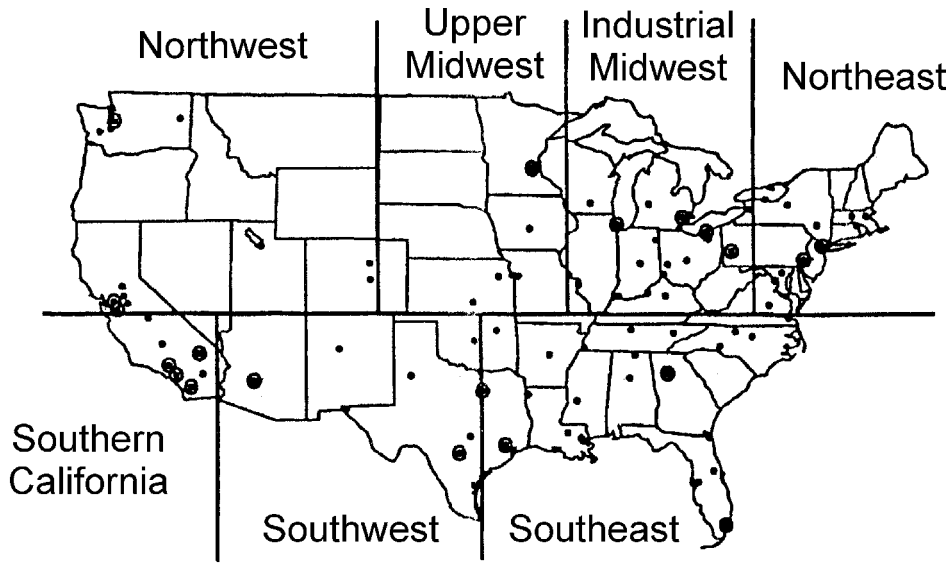

Figure 8-4. Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses.

investigators noted that the extent of the regional heterogeneity in the reanalysis result was reduced slightly compared to the original finding (between-city standard deviation changed from 0.112 to 0.088 in the unit of percent excess deaths per 10 $\mu g/m^3$ PM_{10}), but the pattern of heterogeneity remained the same. The overall national combined estimate (i.e., at lag 1 day, 1.4% excess total deaths per 50 $\mu g/m^3$ increase in PM_{10} using GAM with stringent convergence criteria) for the 90 cities is somewhat lower than the range of estimates for the cities reported in the 1996 PM AQCD.

In the original 90 cities study, the weighted second-stage regression included five types of county- specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude mortality rate); (3) sociodemographic variables (% not graduating from high school and median household income);(4) urbanization (public transportation); and (5) variables related to measurement error (median of all pair-wise correlations between monitors). Some of these variables were apparently correlated (e.g., mean PM_{10} and NO_2, household income and education) so that the sign of coefficients in the regression changed when correlated variables were included in the model. Thus, while some of the county-specific variables were statistically significant (e.g., mean NO_2 levels), interpreting the role of these county-specific variables may

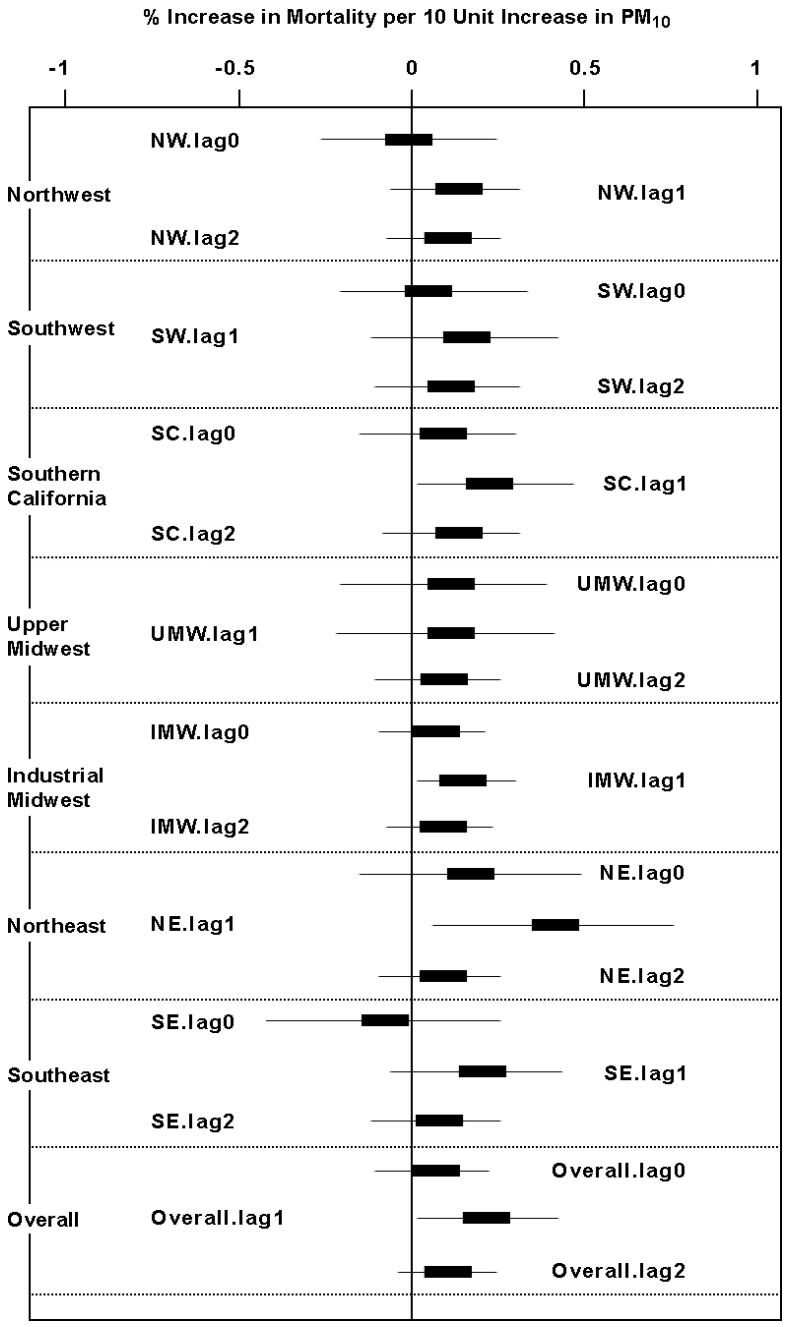

Figure 8-5. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-μg/m^3 increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 8-4.

Source: Dominici et al. (2002; 2003).

require caution. Regarding the heterogeneity of PM_{10} coefficients, the investigators concluded that they "did not identify any factor or factors that might explain these differences."

Another important finding from Samet and coworkers' analyses was the weak influence of gaseous co-pollutants on the PM_{10} effect size estimates (see Figure 8-6). In the reanalysis of 90 cities data, PM_{10} coefficients slightly increased when O_3 was added to regression models. Additions of a third pollutant (i.e., PM_{10} + O_3 + another gaseous pollutant) hardly changed the posterior means of PM_{10} effect size estimates, but widened the distribution. However, the posterior probabilities that the overall PM_{10} effects are greater than zero remained at or above 0.96. The gaseous pollutants themselves in single-, two-, and three-pollutant models were less consistently associated with mortality than PM_{10}. Ozone was not associated with mortality using year-round data; but, in season-specific analyses, it was associated with mortality negatively in winter and positively in summer. SO_2, NO_2, and CO were weakly associated with mortality, but additions of PM_{10} and other gaseous pollutants did not always reduce their coefficients, possibly suggesting their independent effects. As noted in Section 8.1, CO and NO_2 from motor vehicles are likely confounders of $PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the coarse particle fraction. The investigators stated that the PM_{10} effect on mortality "was essentially unchanged with the inclusion of either O_3 alone or O_3 with additional pollutants."

The reanalyses of the 90 cities data by the original NMMAPS investigators also included a sensitivity analysis of lag 1day PM_{10} GLM results to the alternative degrees of freedom for adjustment of the confounding factors: season, temperature, and dewpoint. The degrees of freedom for each of these three smoothing terms was either doubled or halved, resulting in nine scenarios in addition to the degrees of freedom in the original GLM model. The PM_{10} effect posterior means were generally higher when the degrees of freedom were halved for season, and lower when they were doubled, ranging between 1.6% to 0.9% (the main GLM result was 1.1%) excess total mortality per 50 $\mu g/m^3$ PM_{10} increase. These results underscore the fact that the magnitude of sensitivity of the results due to model specification (in this case, degrees of freedom alone) can be as great as the potential bias caused by the GAM convergence problem.

HEI (2003a) states that the revised NMMAPS 90 individual-city mortality results show that, in general, the estimates of PM effect are shifted downward and the confidence intervals are widened. In the revised analyses, a second stage meta-analysis was used to combine results on effects of PM and other pollutants on health outcomes across cities. Tightening the convergence

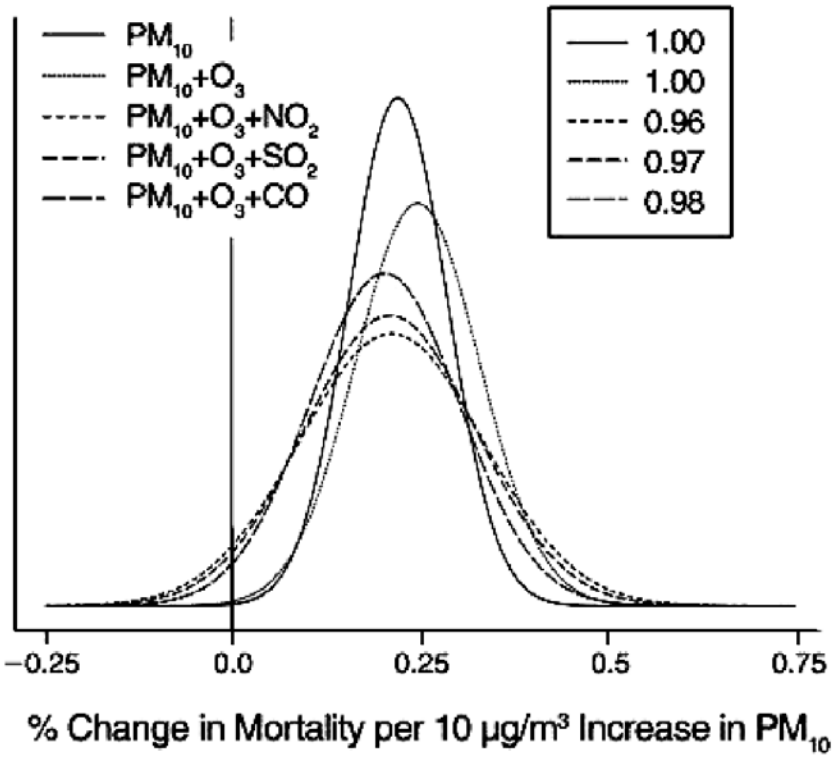

Figure 8-6. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1 with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Dominici et al. (2003).

criteria in GAM obtained a substantially lower estimate of effect of PM_{10} combined over all cities, and use of GLM with natural splines decreased the estimate further. The revised analyses yielded a small, but statistically significant, effect of PM_{10} at lag 1 on total mortality, now estimated to be 0.21% per 10 µg/m^3, with a posterior standard error of 0.06%. HEI (2003a) agrees with the investigators' conclusions that the qualitative conclusions of NMMAPS II have not changed although the evidence for an effect of PM_{10} at lag 0 and lag 2 is less convincing under the new models. The NMMAPS II report found that the PM_{10} effect remained when copollutants were introduced into the model (Samet et al., 2000a); and this conclusion has not changed.

The extent of reduction in PM_{10} excess risk estimate due to the change in the convergence criteria (2.3% per 50 $\mu g/m^3$ PM_{10} using default versus 1.4% using stringent) using GAM models in the 90 cities study appears to be greater than those reported in most of other reanalysis studies. This may be in part due to the smaller risk estimate (2.3%) in the original study compared to other studies (> 3%), as the smaller coefficient is likely more strongly affected as a relative reduction. This may also be in part due to the more "aggressive" adjustment for possible weather effects (discussed later) used in this study, which may have increased the concurvity between PM and the covariates (which included four smoothing terms for weather adjustment). Dominici et al. (2002) reported that the higher the concurvity, the larger the potential bias that a GAM model with default convergence criteria could produce.

In summary, the 90-cities NMMAPS study provides extremely useful information regarding the following: (1) the magnitude of combined PM_{10} risk estimate; (2) the lack of sensitivity of PM_{10} risk estimates to gaseous co-pollutants; (3) indications of some regional heterogeneity in PM_{10} risk estimates across the U.S.; (4) the shape of concentration-response relationship (discussed in a later section); and (5) the range of sensitivity of PM_{10} risk estimates to the extent of smoothing of covariates in their original weather model specification. One major uncertainty that has not been examined in this study is the sensitivity of the PM_{10} risk estimates to different weather model specifications (e.g., use of two temperature terms, rather than four).

U.S. 10-Cities Studies

In another set of multi-city analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000), Zanobetti and Schwartz (2000), Braga et al. (2000), and Braga et al. (2001) analyzed 1987-1995 air pollution and mortality data from ten U.S. cities (New Haven, CT; Birmingham, AL; Pittsburgh, PA; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of these cities was based on the availability of daily (or near daily) PM_{10} data. All of these original studies utilized GAM Poisson models with default convergence criteria. Of these studies, Schwartz (2003) reanalyzed the data from Schwartz (2000a), Schwartz (2000b), and Braga et al. (2001) using GAM with stringent convergence criteria as well as alternative models such as GLM with natural cubic splines or penalized splines, both of which are expected to give correct standard errors. The main original results of the study were presented in the Schwartz (2000a)

paper; and the other studies noted above focused on each of several specific issues, including potential confounding, effect modification, distributed lag, and threshold. In this section, the results for the three reanalysis studies noted above are discussed.

In the reanalysis (Schwartz, 2003b) of the main results (Schwartz, 2000a), daily total (non-accidental) mortality in each of the 10 cities was fitted using a GAM Poisson model (with stringent convergence criteria) or a GLM Poisson model with natural splines, adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time. The data were also analyzed by season (November through April as heating season). The inverse-variance weighted averages of the ten cities' estimates were used to combine results. PM_{10} (average of lag 0 and 1 days) was significantly associated with total deaths, and the effect size estimates were comparable in summer and winter. Adjusting for other pollutants did not substantially change the PM_{10} effect size estimates. The combined percent-excess-death estimate for total mortality was 3.4% (95% CI = 2.6 – 4.1) per 50 $\mu g/m^3$ increase in the average of lag 0 and 1 days PM_{10} (essentially unchanged from the original study) using GAM with stringent convergence criteria. The PM_{10} risk estimate using GLM with natural splines was 2.8% (95% CI = 2.0 – 3.6).

In the reanalysis (Schwartz, 2003b) of the study of multi-day effects of air pollution (Schwartz, 2000b), constrained (quadratic model over 0 through 5 day lags) and unconstrained (0 through 5 day lags) distributed lag models were fitted in each city. The overall estimate was computed using the inverse-variance weighted average of individual city estimates. Among the results obtained using GAM with stringent convergence criteria, the PM_{10} effect size estimate was 6.3% (95% CI = 4.9 – 7.8) per 50 $\mu g/m^3$ increase for the quadratic distributed lag model, and 5.8% (95% CI = 4.4 – 7.3) for the unconstrained distributed lag model. Corresponding values using the penalized splines were somewhat smaller (~ 5.3%). These values are about twice the effect-size estimate for single-day PM_{10} in the original report or the two-day mean PM_{10} reported in the reanalysis above (this reanalysis did not report results for single-day or 2-day mean PM_{10}). These results suggest a possibility that PM effects may be underestimated when only single-day PM indices are used.

Schwartz (2003b) also reanalyzed the data from Braga et al.'s (2001) study to examine the lag structure of PM_{10} association with specific cause of mortality in the 10 cities. Unconstrained distributed lags for 0 through 5 days as well as two-day mean were fitted in each city for COPD, pneumonia, all cardiovascular, and myocardial infarction deaths using GAM with stringent

convergence criteria and penalized spline models. Combined estimates by lag were obtained across the 10 cities. The distributed lag estimates were generally larger than the two-day mean estimates for COPD and pneumonia mortality, but they were comparable for all cardiovascular and myocardial infarction mortality. For example, in the results using GAM with stringent convergence criteria, the PM_{10} effect size estimate was 11.0% (95% CI = 7.2 – 14.8) per 50 $\mu g/m^3$ increase for two-day mean model, and 16.8% (95% CI = 8.3 – 25.9) for the unconstrained distributed lag model. Note that these values are substantially larger than those reported for total non-accidental deaths.

The PM_{10} risk estimates from these 10 cities studies appear to be larger than those from the 90 cities study. Aside from the difference in the number of cities analyzed, the difference in weather model specification and the extent of smoothing for temporal trends may have contributed to the difference in the size of PM_{10} risk estimates. This issue is further discussed in Section 8.2.2.3.5.

Reanalyses of Harvard Six Cities Study

Both the original Harvard Six Cities Study time-series analysis (Schwartz et al., 1996a) and the replication analysis by Klemm et al. (2000), which essentially replicated Schwartz et al.'s original findings, used GAM Poisson models with default convergence criteria. Schwartz (2003a) and Klemm and Mason (2003) conducted reanalyses of the Harvard Six Cities data to address the GAM statistical issues.

Schwartz (2003a) reported the risk estimates for $PM_{2.5}$ only, but provided results using several other spline smoothing methods (natural splines, B-splines, penalized splines, and thin plate splines) in addition to GAM with stringent convergence criteria. The risk estimate combined across the six cities per 25 $\mu g/m^3$ in $PM_{2.5}$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria was 3.5% (95% CI = 2.5 – 4.5), as compared to the original value of 3.7% (95% CI = 2.7 – 4.7). The corresponding value from a GLM model with natural splines was 3.3% (95% CI = 2.2 – 4.3). The values using B-splines, penalized splines, and thin plate splines were somewhat lower (3.0%, 2.9%, and 2.6%, respectively). However, when the Harvard Six Cities were examined individually in the reanalysis of Schwartz using GLM and penalized splines, Boston and St. Louis gave significant associations with $PM_{2.5}$ and Steubenville gave a significant association with coarse PM.

Klemm and Mason's reanalysis (2003) reported risk estimates for $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (PM_{15} or PM_{10}), and SO_4^{-2}. They also conducted sensitivity analyses using GLM with natural splines that approximated the degrees of freedom used in the LOESS smoothers in the GAM models, as well as 12 knots per year and 4 knots per year for smoothing of temporal trends. The $PM_{2.5}$ and $PM_{10-2.5}$ total non-accidental mortality risk estimates combined across the six cities per 25 $\mu g/m^3$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria were 3.0% (95% CI = 2.1 – 4.0) and 0.8% (95% CI = –0.5, 2.0), respectively. The corresponding PM_{10} mortality excess risk estimate per 50 $\mu g/m^3$ (average of lag 0 and 1 day) was 3.6% (95% CI = 2.1, 5.0). In their sensitivity analysis, increasing the degrees of freedom for temporal trends for natural splines in GLM models from 4 knots/year to 12 knots/year markedly reduced PM risk estimates. For example, the $PM_{2.5}$ risk estimate per 25 $\mu g/m^3$ was reduced from 2% in the 4 knots/year model to 1% in the 12 knots/year model. The results showing the smaller PM risk estimates for larger degrees of freedom for smoothing of temporal trends are consistent with similar findings reported for the reanalysis of 90 cities study.

Although PM effect estimates from the Klemm and Mason (2003) reanalysis are somewhat smaller than those from Schwartz (2003; e.g., 3.5% by Schwartz versus 3.0% by Klemm and Mason for $PM_{2.5}$ using strict convergence criteria), the results are essentially comparable. Both studies also showed that the comparable GLM models produced smaller risk estimates than GAM models.

U.S. 3-Cities Study

Moolgavkar (2000a) evaluated associations between short-term measures of major air pollutants and daily deaths in three large U.S. metropolitan areas (Cook Co., IL, encompassing Chicago; Los Angeles Co., CA; and Maricopa Co., AZ, encompassing Phoenix) during a 9-year period (1987-1995). Moolgavkar (2003) reanalyzed the data for Cook Co. and Los Angeles Co., but not Maricopa Co. using GAM with stringent convergence criteria as well as GLM with natural splines. Ozone was analyzed in the original analysis but not in the reanalysis (it was only positive and significant in Cook county in the original analysis). This section describes the results from the reanalysis. Total non-accidental deaths, deaths from cardiovascular disease (CVD) and chronic obstructive lung disease (COPD) were analyzed in relation to 24-h readings for PM, CO, NO_2, and SO_2 averaged over all monitors in a given county. Cerebrovascular

mortality was analyzed in the original analysis but not in the reanalysis (its association with air pollution was weak in the original analysis). The results of cause-specific mortality analyses are described in a later section. Daily readings were available for each of the gaseous pollutants in both Cook Co. and Los Angeles Co., as were PM_{10} values for Cook Co. However, PM_{10} and $PM_{2.5}$ values were only available every sixth day in Los Angeles Co. PM values were highest in summer in Cook Co. and in the winter and fall in Los Angeles Co.; whereas the gases (except for O_3) were highest in winter in both counties. The PM indices were moderately correlated ($r = 0.30$ to 0.73) with CO, NO_2, and SO_2 in Cook Co. and Los Angeles Co. Total non-accidental, CVD, and COPD deaths were all highest during winter in both counties.

Adjusting for temperature and relative humidity effects in separate analyses for each mortality endpoint for these two counties, varying patterns of results were found, as noted in Table 8A-1. Moolgavkar (2003) also reported sensitivity of results to different degrees of freedom (df) for smoothing of temporal trends (30 df and 100 df).

As for Cook Co. results, PM_{10} was significantly associated with total non-accidental mortality at lag 0 (most significant) and 1 day in GAM models with both 30 df and100 df for smoothing of temporal trends, as well as in a GLM model with 100 df for smoothing of temporal trends. The gaseous pollutants were also significantly associated with total non-accidental mortality at various lags (wider lags than PM_{10}), but most significant at lag 1 day. These associations did not appear to be sensitive to the extent of smoothing for temporal trends, at least at their most significant lags. In two pollutant models (results were not shown in tables but described in text), the PM_{10} association remained "robust and statistically significant" at lag 0 day; whereas the coefficients for the gases became non-significant. However, at lag 1 day, the PM_{10} association became non-significant and the gases remained significant. Thus, some extent of "sharing" of the association is apparent, and whichever pollutant is more strongly associated than the other at that lag tended to prevail in the two pollutant models in this data set.

For Los Angeles Co., CO was more significantly associated (positive and significant at lag 0 through 3 days) with mortality than PM_{10} (positive and significant at lag 2) or $PM_{2.5}$ (positive and significant at lag 1). In two pollutant models in which CO and PM indices were included simultaneously at PM indices' "best" lags, CO remained significant; whereas PM coefficients became non-significant (and negative for cases with 30 df for temporal smoothing). For Los Angeles data, the PM coefficients appeared to be more sensitive to the choice of the degrees of

freedom than to the default versus stringent convergence criteria. GLM models tended to produce smaller risk estimates than GAM models. Moolgavkar also reported that these associations were robust to varying the extent of smoothing for weather covariates.

The results for these two cities do not reflect a common pattern. In Cook Co., all the pollutants were associated with mortality, and their relative importance varied depending on the lag day; whereas CO showed the strongest mortality associations in Los Angeles. Moolgavkar concluded that, considering the substantial differences that can result from different analytic strategies, no particular numeric estimates were too meaningful, although the patterns of associations appeared to be robust.

8.2.2.3.2 Canadian Multicity Studies

Burnett et al. (2000) analyzed various PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, CoH, and 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO) for association with total mortality in the 8 largest Canadian cities: Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This study differs from Burnett et al. (1998a) in that it included fewer cities but more recent years of data (1986-1996 versus 1980-1991) and detailed analyses of particle mass components by size and elemental composition. Each city's mortality, pollution, and weather variables were separately filtered for seasonal trends and day-of-week patterns. The residual series from all cities were then combined and analyzed in a GAM Poisson model. In Burnett and Goldberg's reanalysis (2003) of the eight cities data, they only examined the PM indices $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} using GAM models with more stringent convergence criteria. The reanalysis used co-adjustment regression (i.e., simultaneous regression), rather than the regression with pre-filtered data that was the main approach of the original analysis. The reanalysis also considered several sensitivity analyses including models with and without day-of-week adjustment and several alternative approaches (fitting criteria and extent of smoothing) to adjust for temporal trends using natural splines.

Adjusting for temporal trends, smoothing of same-day temperature, pressure, and day-of-week effects, the pooled PM effect estimates across the eight Canadian cities were: 3.7% (95% CI = 1.4-6.0) per 25 $\mu g/m^3$ increase in $PM_{2.5}$; 2.1% (0.1-4.2) per 25 $\mu g/m^3$ increase $PM_{10-2.5}$; and 3.6% (95% CI = 1.3-5.8) per 50 $\mu g/m^3$ increase PM_{10}. These effect size estimates are fairly close

to the estimates reported in the original study, despite the differences in the regression approach (pre-filtering and GAM with default convergence criteria in the original study versus co-adjustment and using GAM with stringent convergence criteria). The temporal adjustment of the above model used LOESS smoothing with span of approximately 0.022 (= 90 days/4012 study days). Sensitivity analysis included several choices of degrees of freedom for natural splines of temporal trend, with two fitting criteria (i.e., Bartlett's test for white noise and AIC) and either using the same degrees of freedom for all the eight cities or varying degrees of freedom for each city. The PM risk estimates based on natural splines were generally smaller than those based on LOESS smoothers. The PM risk estimates also varied inversely with the number of knots for temporal trend. That is, the more details of the temporal trend were described by natural splines, the smaller the PM risk estimates became. The reported $PM_{2.5}$ risk estimates per 25 $\mu g/m^3$ increase were 3.0% (t=3.12), 2.8% (t=2.28), 2.2% (t=2.14), 2.1% (t=2.07), and 1.9% (t=1.72) for knot/year, knot/6 months, knot/3 months, knot/2 months, and knot/1 month, respectively. The corresponding values for 25 $\mu g/m^3$ increase in $PM_{10-2.5}$ were 3.9% (t=3.42), 2.9% (t=2.52), 2.1% (t=1.69), 1.8% (t=1.46), and 1.2% (t=0.91), suggesting greater sensitivity of $PM_{10-2.5}$ risk estimates to the extent of temporal smoothing. The authors suggested that this was likely due to the stronger correlation between (and temporal trends in) mortality and mass concentrations for $PM_{10-2.5}$ (average correlation among cities of –0.45) than for $PM_{2.5}$ (–0.36). Because the relative significance and size of $PM_{2.5}$ and $PM_{10-2.5}$ risk estimates varied depending on the model and extent of smoothing for temporal trend, it is difficult to determine the relative importance of the two size-fractionated PM indices in this study.

8.2.2.3.3 European Multi-City APHEA Study Analyses

The Air Pollution and Health: A European Approach (APHEA) project is a multi-center study of short-term effects of air pollution on mortality and hospital admissions within and across a number of European cities having a wide range of geographic, climatic, sociodemographic, and air quality patterns. The obvious strength of this approach is its ability to evaluate potential confounders or effect modifiers in a consistent manner. It should be noted that PM indices measured in those cities varied. In APHEA1, the PM indices measured were mostly black smoke (BS), except for Paris, Lyon (PM_{13}); Bratislava, Cologne, and Milan (TSP); and Barcelnoa (BS and TSP). In APHEA2, 10 out of the 29 cities used actual PM_{10} measurements;

and, in 11 additional cities, PM_{10} levels were estimated based on regression models relating collocated PM_{10} measurements to BS or TSP. In the remaining 8 cities, only BS measurements were available (14 cities had BS measurements). As discussed below, there have been several papers published that present either a meta-analysis or pooled summary estimates of these multi-city mortality results: (1) Katsouyanni et al. (1997) — SO_2 and PM results from 12 cities; (2) Touloumi et al. (1997) — ambient oxidants (O_3 and NO_2) results from six cities; (3) Zmirou et al. (1998) — cause-specific mortality results from 10 cities (see Section 8.2.2.5); (4) Samoli et al. (2001) — a reanalysis of APHEA1 using a different model specification (GAM) to control for long-term trends and seasonality; and (5) Katsouyanni et al. (2001) — APHEA2, with emphasis on the examination of confounding and effect modification. The original APHEA protocol used sinusoidal terms for seasonal adjustment and polynomial terms for weather variables in Poisson regression models. Therefore, publications 1 through 3 above are not subject to the GAM default convergence issue. Publications 4 and 5 did use GAM Poisson model with default convergence criteria, but the investigators have reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines (Katsouyani et al., 2003; Samoli et al., 2003). The discussions presented below on publications 4 and 5 are focused on the results from the reanalyses.

APHEA1 Sulfur Dioxide and Particulate Matter Results for 12 Cities

The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens, Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyons, Milan, Paris, Poznan, and Wroclaw. In the western European cities, an increase of 50 $\mu g/m^3$ in SO_2 or BS was associated with a 3% (95% CI = 2.0, 4.0) increase in daily mortality; and the corresponding figure was 2% (95% CI = 1.0, 3.0) for estimated PM_{10} (they used conversion: PM_{10} = TSP*0.55). In the 31 central/eastern European cities, the increase in mortality associated with a 50 μ g/m^3 change was 0.8% (CI = 0.1, 2.4) for SO_2 and 0.6% (CI = 0.1, 1.1) per 50 $\mu g/m^3$ change in BS. Estimates of cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to those for one day effects. The effects of both pollutants (BS, SO_2) were stronger during the summer and were mutually independent. Regarding the contrast between the western and central/eastern Europe results, the authors speculated that this could be due to differences in exposure representativeness; differences in pollution toxicity or mix; differences in proportion of

sensitive sub-population; and differences in model fit for seasonal control. Bobak and Roberts (1997) commented that the heterogeneity between central/eastern and western Europe could be due to the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted that, having examined the source of heterogeneity, other factors could apparently explain the difference in estimates as well as or better than temperature.

APHEA1 Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities

Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents), and (b) impacts on effect estimates for NO_2 and O_3 of including a PM measure (BS) in multi-pollutant models. Six cities in central and western Europe provided data on daily deaths and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were fitted. Significant positive associations were found between daily deaths and both NO_2 and O_3. Increases of 50 $\mu g/m^3$ in NO_2 (1-hour maximum) or O_3 (1-hour maximum) were associated with a 1.3% (95% CI = 0.9-1.8) and 2.9% (95% CI = 1.0-4.9) increase in the daily mortality, respectively. There was a tendency for larger effects of NO_2 in cities with higher levels of BS: when BS was included in the model, the coefficient for NO_2 was reduced by half (but remained significant) whereas the pooled estimate for the O_3 effect was only slightly reduced. The authors speculated that the short-term effects of NO_2 on mortality might be confounded by other vehicle-derived pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study reports only relative risk levels for NO_2 and O_3 (but not for BS), it illustrates the importance of confounding of NO_2 and PM effects and the relative limited confounding of O_3 and PM effects.

APHEA1: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality

The original study (Samoli et al., 2001) attempted to examine the sensitivity of APHEA1 results to how the temporal trends were modeled (i.e., sine/cosine in the APHEA1 versus LOESS smoother using GAM with default convergence criteria). Samoli et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines. Thus, the reanalysis allowed a comparison of results across a fixed functional model (sine/cosine), a non-parametric smoother (GAM with LOESS), and a parametric smoother (GLM

with natural splines). The combined estimate across cities for percent excess in total non-accidental mortality per 50 μg/m^3 increase in BS using GAM with stringent convergence criteria (2.3%; 95% CI = 1.9-2.7) was bigger than that using sine/cosine (1.3%; 95% CI = 0.9-1.7). The GAM with stringent convergence criteria reduced the combined estimate by less than 10% compared to that from GAM with default convergence criteria. The corresponding estimate using GLM with natural splines (1.2%; 95% CI = 0.7-1.7) was comparable to that from the sine/cosine model but smaller than that using GAM. The contrast between western and eastern Europe in the original APHEA1 study (2.9% for west versus 0.6% for east) was less clear in the results using GAM with stringent convergence criteria (2.7% versus 2.1%) or GLM with natural splines (1.6% versus 1.0%). These results indicate that the apparent regional heterogeneity found in the original APHEA1 study could be sensitive to model specification. Because the number of cities used in the APHEA1 study 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. These reanalysis results also suggest that the results are somewhat sensitive to the model specification of temporal trends.

APHEA2: Confounding and Effect Modification Using Extended Data

The APHEA2 original study (Katsouyanni et al. 2001) included more cities (29 cities) and a more recent study period (variable years in 1990-1997, as compared to 1975-1992 in APHEA1). Also, the APHEA2 original study used a GAM (with default convergence criteria) Poisson model with LOESS smoothers to control for season and trends. Katsouyanni et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria, as well as two parametric approaches: natural splines and penalized splines. Because the reanalysis GAM results changed the PM_{10} risk estimates only slightly from the original estimates and the investigators mention that the patterns of effect modification were preserved in their reanalyses regardless of model specification, the qualitative description of the effect modification below relies on the original study. The PM_{10} estimates for various models are from the reanalysis results.

The analyses put emphasis on effect modification by city-specific factors. Thus, the city-specific coefficients from the first stage of Poisson regressions were modeled in the second stage regression using city-specific characteristics as explanatory variables. Inverse-variance

weighted pooled estimates (fixed-effects model) were obtained as part of this model. When substantial heterogeneity was observed, the pooled estimates were obtained using random-effects models. These city-specific variables included (1) air pollution level and mix, such as average air pollution levels and PM/NO_2 ratio (as an indicator of traffic-generated PM); (2) climatic variables, such as mean temperature and relative humidity; (3) health status of the population, such as the age-adjusted mortality rates, the percentage of persons over 65 years of age, and smoking prevalence; and (4) geographic area (three regions: central-eastern, southern, and north-western). The study also addressed the issue of confounding by simultaneous inclusion of gaseous co-pollutants in city-specific regressions and obtained the pooled PM estimates for each co-pollutant included. Unlike APHEA1, in which the region (larger PM estimates in western Europe than in central-eastern Europe) was highlighted as the important factor, APHEA2 found several effect modifiers. NO_2 (i.e., index of high pollution from traffic) was an important one. The cities with higher NO_2 levels showed larger PM effects as did the cities with a warmer climate. The investigators noted that this might be due to the better estimation of population exposures with outdoor community monitors (because of more open windows). Also, the cities with low standardized mortality rate showed larger PM effects. The investigators speculated that this may be because a smaller proportion of susceptible people (to air pollution) are available in a population with a large age-standardized mortality rate. Interestingly, in the pooled PM risk estimates from models with gaseous pollutants, it was also NO_2 that affected (reduced) PM risk estimates most. For example, in the fixed-effects models, approximately 50% reductions in both PM_{10} and BS coefficients were observed when NO_2 was included in the model. SO_2 only minimally reduced PM coefficients; whereas O_3 actually increased PM coefficients. Thus, in this analysis, NO_2 was implicated both as a confounder and an effect modifier. The overall random-effects model combined estimate for total mortality for 50 $\mu g/m^3$ increase in PM_{10} were 3.0% (95% CI = 2.0, 4.1), 2.1% (95% CI = 1.2, 3.0), and 2.8% (95% CI = 1.8, 3.8), for GAM (stringent convergence criteria), natural splines, and penalized splines models, respectively. The original estimate using GAM with default convergence criteria (3.1%) was thus reduced by 4%. While the effect estimates varied somewhat depending on the choice of GAM with LOESS, natural splines, or penalized splines, the investigators reported that the patterns of effect modification (by NO_2, etc.) were preserved.

8.2.2.3.4 Comparison of Effects Estimates from Multi-City Studies

Based on different pooled analyses of data combined across multiple cities, the percent excess (total, non-accidental) deaths estimated per 50 $\mu g/m^3$ increase in PM_{10} in the above multi-city studies were (1) 1.4% using GAM (1.1% using GLM) at lag 1-day in the 90 largest U.S. cities (the Northeast region results being about twice as high); (2) 3.4% using GAM (2.8% using GLM) for average of 0 and 1 day lags in 10 U.S. cities; (3) 3.6% using GAM (2.7% using GLM) for 1 day lag PM_{10} in the 8 largest Canadian cities; and (4) 3.0% using GAM (2.1% using GLM) in APHEA2 for average of 0 and 1 day lags for 29 European cities during 1990-1997.

Note that the estimate for the NMMAPS 90 cities study is somewhat smaller than those for the rest of the multi-city studies and the range reported in the previous PM AQCD (2.5 to 5%). There may be several possible explanations for this, but model specification for weather is likely one major factor. The 90 cities study used much more "aggressive" adjustment for possible weather effects than most studies. The 90 cities analysis included four separate weather terms: (1) smoothing splines (natural splines when GLM was used) of same-day temperature with 6 degrees of freedom; (2) smoothing splines of the average of lag 1 through 3 day temperature with 6 degrees of freedom; (3) smoothing splines of same-day dewpoint with 3 degrees of freedom; and, (4) smoothing splines of the average of lag 1 through 3 day dewpoint with 3 degrees of freedom. In contrast, most of the other studies used only one or two terms for weather variables. For example, the Harvard Six Cites Study used a LOESS smoother (or natural splines or other smoothers in reanalysis) of same-day temperature with a span of 0.5 and a LOESS smoother of same-day dewpoint with a span of 0.5. Note that the 90 cities study not only used more terms for weather effects, but it also used more degrees of freedom for temperature than Schwartz et al.'s analysis (according to Klemm and Mason's reanalysis, the span of 0.5 in LOESS corresponds to approximately 3.5 degrees of freedom). It should also be noted here that the purpose of the inclusion of dewpoint in these models is often explained as "to adjust for possible effects of humidity"; but, in fact, dewpoint and temperature are highly correlated ($r > 0.9$) in most cities. Thus, although the inclusion of these terms may statistically (i.e., by AIC, etc.) provide a better fit, the epidemiologic implications of the use of these terms is not yet clear. While extreme temperature, hot or cold, is known to cause excess mortality, it is not clear at this time whether these models are adequately modeling the weather effects in the more moderate range (which is much of the data). Thus, the inclusion in the NMMAPS

modeling of several weather terms with more degrees of freedom most likely provides "conservative" PM risk estimates. That is, the NMMAPS excess risk estimates of 1.1% or 1.4% per 50 $\mu g/m^3$ PM_{10} increase may well underestimate the PM_{10}-total mortality effect-size suggested by two other well conducted multicity studies to fall in the range of 2.7% to 3.6% per 50 $\mu g/m^3$ PM_{10} increment for U.S. and Canadian cities.

Another factor that may contribute to the difference in PM risk estimates is the extent of smoothing to adjust for temporal trends. Several of the reanalysis studies (Dominici et al., 2002; Burnett and Goldberg, 2003; Ito, 2003; Klemm and Mason, 2003; Molgavkar, 2003) consistently reported, though to varying extents, that using more degrees of freedom for temporal trends tended to reduce PM coefficients. That is, when more details in the short-term fluctuations of mortality were ascribed to temporal trends, PM risk estimates were reduced. For example, in Dominici et al.'s (2002) sensitivity analysis, the PM_{10} risk estimate was larger (1.6% per 50 $\mu g/m^3$ increase in PM_{10}) for the GLM model with 3 degrees of freedom per year that the estimate using 7 degrees of freedom (1.1%). Note that, in general, the presumed objective of including temporal trends in the mortality regression is to adjust for potential confounding (measured or unmeasured) by time-varying factors that change seasonally or in shorter time spans (e.g., influenza epidemics). However, ascribing "too short" temporal fluctuations to these "confounding temporal trends" may inadvertently take away PM effects. Because the "right" extent of smoothing is not known, these sensitivity analyses are useful. In the reanalyses mentioned above, the PM risk estimates could change by a factor of two when a range of degrees of freedom was applied even for a model specification in which all the other terms were kept unchanged.

Based on the results from the reanalysis studies, it has become apparent that different smoothing approaches can also affect PM risk estimates. For example, the models with natural splines (parametric smoothing) appear, in general but not always, to result in smaller PM risk estimates than GAM models with LOESS or smoothing splines. GAM models may possibly suffer from biased standard error of risk estimates, but they also seem to fit the data better (i.e., based on AIC) than GLM models with natural splines. Thus, it is not clear which smoothers provide the most appropriate PM risk estimates. In any case, the choice of these smoothers does not seem to affect PM risk estimates (~ 10 to 30%) as much as the range of weather model

specifications or the range of the degrees of freedom for temporal trends adjustment do (as large as a factor of two).

A less explored issue is the effect of multi-day effects of PM. The PM_{10} risk estimates summarized above are either for a single-day lag (U.S. 90 cities study, Canadian 8 cities study, and APHEA1), or an average of two days (U.S. 10 cities study and APHEA2). However, the reanalysis of U.S. 10 cities study data suggests that the multi-day PM effect, accounting for 0 through 5 day lag, could be twice as large as the effect sizes estimated from single or two-day average models and even bigger (~ 3 to 4 fold) when more specific cause of death categories were examined. This issue warrants further investigation.

In summary, considering all the options in model specifications that can affect the PM risk estimates, the reported combined PM_{10} total non-accidental mortality risk estimates from multi-city studies are in good agreement, in the range of 1.0 to 3.5% per 50 $\mu g/m^3$ increase in single or two-day average PM_{10}. The U.S. 90 cities study provides estimates towards the lower end of this range. Combinations of choices in model specifications (the number of weather terms and degrees of freedom for smoothing of mortality temporal trends) alone may explain the extent of the difference in PM_{10} risk estimates across studies. The range for these newly available combined estimates from multi-cities studies overlap with the range of PM_{10} estimates (2.5 to 5%, obtained from single cities studies) previously reported in the 1996 PM AQCD, but extends to somewhat lower values.

8.2.2.4 The Role of Particulate Matter Components

Delineation of the roles of specific ambient PM components in contributing to associations between short-term PM exposures and mortality requires evaluation of several factors, e.g., size, chemical composition, surface characteristics, and the presence of gaseous co-pollutants. While possible combinations of these factors can in theory be limitless, the actual data tend to cover definable ranges of aerosol characteristics and co-pollutant environments due to typical source characteristics (e.g., fine particles tend to be combustion products in most cities). Newly available studies conducted in the last few years have begun to provide more extensive information on the roles of PM components; and their results are discussed below in relation to three topics: (1) PM particle size (e.g., $PM_{2.5}$ versus $PM_{10-2.5}$); (2) chemical components; and (3) source oriented evaluations.

The ability to compare the relative roles of different PM size fractions and various PM constituents is restricted by the limitations of the available studies. Comparisons nevertheless can be attempted, using such information as the relative level of significance and/or the strength of correlation between component estimate and health outcome. The relative significance across cities/studies is influenced by the sample size and the level of the pollutants. The width of the confidence band also needs to be taken into account, according more weight for studies with narrower confidence bands. Caution in interpretation of such information, however, is warranted because of potential measurement error and possible high correlations between indices being compared. Additionally, limitations of single-city studies must be recognized.

8.2.2.4.1 Particulate Matter Particle Size Evaluations

With regard to the relative importance of the fine and coarse fractions of inhalable PM_{10} particles capable of reaching thoracic regions of the respiratory tract, at the time of the 1996 PM AQCD only one acute mortality study (Schwartz et al., 1996a) had examined this issue. That study (which used GAM with default convergence criteria in analyzing Harvard Six-City study data) suggested that fine particles ($PM_{2.5}$), distinctly more so than coarse fraction ($PM_{10-2.5}$) particles, were associated with daily mortality. Recent reanalyses using GAM with more stringent convergence criteria have yielded only slightly smaller $PM_{2.5}$ effect-size estimates (Schwartz et al., 2003). It should also be noted that (a) the Klemm et al. (2000) reanalysis reconstructed the data and replicated the original analyses (using GAM with default convergence criteria) and (b) the Klemm and Mason (2003) reanalysis, using GAM with stringent convergence criteria and GLM with parametric smoothers, also essentially reproduced the original investigators' results.

Since the 1996 PM AQCD, several new studies have used size-fractionated PM data to investigate the relative importance of fine ($PM_{2.5}$) versus coarse ($PM_{10-2.5}$) fraction particles. Table 8-2 provides synopses of those studies with regard to the relative importance of the two size fractions, as well as some characteristics of the data. The average levels of $PM_{2.5}$ ranged from about 13 to 30 $\mu g/m^3$ in the U.S. cities, but much higher average levels were measured in Santiago, Chile (64.0 µg/m3). As can be seen in Table 8-2, in the northeastern U.S. cities (Philadelphia, PA and Detroit, MI), there was more $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average; whereas in the western U.S. (Phoenix, AZ; Coachella Valley, CA; Santa Clara County,

TABLE 8-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10-2.5}$	Results regarding relative importance of $PM_{2.5}$ versus $PM_{10-2.5}$ and comments.
Fairley (1999 & 2003)* Santa Clara County, CA	$PM_{2.5}$ mean = 13; $PM_{2.5}/PM_{10}$ =0.38; r = 0.51.	Of the various pollutants (including PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, CoH, CO, NO_2, and O_3), the strongest associations were found for ammonium nitrate and $PM_{2.5}$. $PM_{2.5}$ was significantly associated with mortality, but $PM_{10-2.5}$ was not, separately and together in the model. Winter $PM_{2.5}$ level is more than twice that in summer. The daily number of O_3 ppb-hours above 60 ppb was also significantly associated with mortality.
Ostro et al. (2000 & 2003)* Coachella Valley, CA	$PM_{2.5}$ (Palm Springs and Indio, respectively) mean = 12.7, 16.8; $PM_{2.5}/PM_{10}$ = 0.43, 0.35; r = 0.46, 0.28.	Coarse particles dominate PM_{10} in this locale. $PM_{2.5}$ was available only for the last 2.5 years; and a predictive model could not be developed, so that a direct comparison of $PM_{2.5}$ and $PM_{10-2.5}$ results is difficult. Cardiovascular mortality was significantly associated with PM_{10} (and predicted $PM_{10-2.5}$), whereas $PM_{2.5}$ was mostly negatively (and not significant) at the lags examined.
Clyde et al. (2000) Phoenix, AZ	$PM_{2.5}$ mean = 13.8; $PM_{2.5}/PM_{10}$ = 0.30; r = 0.65.	Using the Bayesian Model Averaging that incorporates model selection uncertainty with 29 covariates (lags 0- to 3-day), the effect of coarse particle (most consistent at lag 1 day) was stronger than that for fine particles. The association was for mortality defined for central Phoenix area where fine particles ($PM_{2.5}$) are expected to be uniform.
Mar et al. (2000 & 2003)* Phoenix, AZ 1995-1997	$PM_{2.5}$ (TEOM) mean = 13; $PM_{2.5}/PM_{10}$ = 0.28; r = 0.42.	Cardiovascular mortality was significantly associated with both $PM_{2.5}$ (lags 1, 3, and 4) and $PM_{10-2.5}$ (lag 0) with similar effect size estimates. Of all the pollutants (SO_2, NO_2, and elemental carbon were also associated), CO was most significantly associated with cardiovascular mortality.
Smith et al. (2000) Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, the authors found a statistically significant mortality association with $PM_{10-2.5}$, but not with $PM_{2.5}$. In the models allowing for a threshold, they found evidence of a threshold for $PM_{2.5}$ (in the range of 20-25), but not for $PM_{10-2.5}$. A seasonal interaction in the $PM_{10-2.5}$ effect was also reported: the effect is highest in spring and summer when the anthropogenic concentration of $PM_{10-2.5}$ is lowest.
Lippmann et al. (2000); Ito, (2003)* 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 (but not significantly) associated with mortality outcomes to a similar extent. Simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$ also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a) Philadelphia, PA 1992-1995.	$PM_{2.5}$ 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 $PM_{2.5}$ versus $PM_{10-2.5}$ and comments
Klemm and Mason (2000) Atlanta, GA	$PM_{2.5}$ mean = 19.9; $PM_{2.5}/PM_{10}$ = 0.65	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.
Klemm et al. (2000); Klemm and Mason (2003)* 6 U.S. cities	Mean $PM_{2.5}$ ranges from 11.3 to 29.6; Mean $PM_{10-2.5}$ ranges from 6.6 to 16.1; Mean $PM_{2.5}/PM_{10}$ ranges from 50.1% to 66% in the six cities.	This reanalysis of the Harvard Six-Cities time-series analysis by Schwartz et al. (1996a) found significant associations between total mortality and $PM_{2.5}$ in 3 cities and in pooled effect, but no significant association with $PM_{10-2.5}$ in the reanalysis of the replication study for any city. These results essentially confirmed the findings of the original study by Schwartz et al. (1996a).
Chock et al. (2000) Pittsburgh, PA	Data distribution not reported. $PM_{2.5}/PM_{10}$ = 0.67	Seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and the small size of the data set (stratified by age group and season) limit confidence in finding of no consistently significant associations for any size fractions.
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 Canadian cities	$PM_{2.5}$ mean=13.3; $PM_{2.5}/PM_{10}$ =0.51; r = 0.37.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were significantly associated with total non-accidental mortality. Results using varying extent of smoothing of mortality temporal trends show that there is no consistent pattern of either PM mass index being more important. The authors note that $PM_{10-2.5}$ was more sensitive to the type of smother and amount of smoothing.
Cifuentes et al. (2000) Santiago, Chile 1988-1996	$PM_{2.5}$ mean=64.0; $PM_{2.5}/PM_{10}$ =0.58; r = 0.52.	In GLM results for the whole years, only $PM_{2.5}$ and NO_2 were consistently significantly associated with total non-accidental mortality.

Note: * next to author name indicates that the study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms.

CA) the average $PM_{10-2.5}$ levels were higher than $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 8-2 use much the same data set; all used fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal differences in PM component levels should also be noted. For example, in Santa Clara County and in Santiago, Chile, winter $PM_{2.5}$ levels averaged twice those during summer. The temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$ ranged between 0.30 and 0.65. Such differences in ambient PM mix features from season to

season or from location to location complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

To facilitate a quantitative overview of the effect size estimates and their corresponding uncertainties from these studies, the percent excess risks are plotted in Figure 8-7. These excluded the Clyde et al. study (for which the model specification did not obtain RRs for $PM_{2.5}$ and $PM_{10-2.5}$ separately) and the Smith et al. study (which did not present linear term RRs for $PM_{2.5}$ and $PM_{10-2.5}$). Note that, in most of the original studies, the RRs were computed for comparable distributional features (e.g., interquartile range, mean, 5^{th} -to-95^{th} percentile, etc.). However, the increments derived and their absolute values varied across studies; therefore, the RRs used in deriving the excess risk estimates delineated in Figure 8-7 were re-computed for consistent increments of 25 $\mu g/m^3$ for both $PM_{2.5}$ and $PM_{10-2.5}$. Note also that re-computing the RRs per 25 $\mu g/m^3$ in some cases changed the relative effect size between $PM_{2.5}$ and $PM_{10-2.5}$, but it did not affect the relative significance. All of the studies found positive associations between both the fine and coarse PM indices and increased mortality risk. However, most of the studies did not have large enough sample sizes to separate out what often appear to be relatively small differences in effect size estimates; but two of the studies do show distinctly larger mortality associations with $PM_{2.5}$ than for non-significant $PM_{10-2.5}$ effects. For example, the Klemm et al. (2000) and Klemm and Mason's (2003) re-computation of the Harvard Six Cities time-series study reconfirmed the original Schwartz et al. (1996a) finding that $PM_{2.5}$ was significantly associated with excess mortality, but $PM_{10-2.5}$ across all cities was not (although the Schwartz [2003a] reanalyses reconfirmed the original findings of statistically significant $PM_{10-2.5}$-mortality relationship in Steubenville, OH). Similar findings of $PM_{2.5}$ being significantly associated with mortality were obtained in Santa Clara County (Fairley, 1999; Fairley 2003). Two studies suggested that $PM_{10-2.5}$ was more important than $PM_{2.5}$: Coachella Valley, CA (Ostro et al., 2000 & 2003) and Phoenix, AZ (Clyde et al., 2000). There were five studies in which the importance of $PM_{2.5}$ and $PM_{10-2.5}$ were considered to be similar or, at least, not distinguishable: Philadelphia, PA (Lipfert et al., 2000a); Detroit, MI (Lippmann et al., 2000; reanalysis by Ito 2003); Phoenix, AZ (Mar et al., 2000 and reanalysis in 2003); Eight Canadian cities (Burnett at al., 2000; reanalysis by Burnett and Goldberg, 2003); and Santiago, Chile (Cifuentes et al., 2000).

In the reanalysis (Burnett and Goldberg, 2003) of the Canadian 8-city study (Burnett et al., 2000), the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ was not clear, but both PM indices were

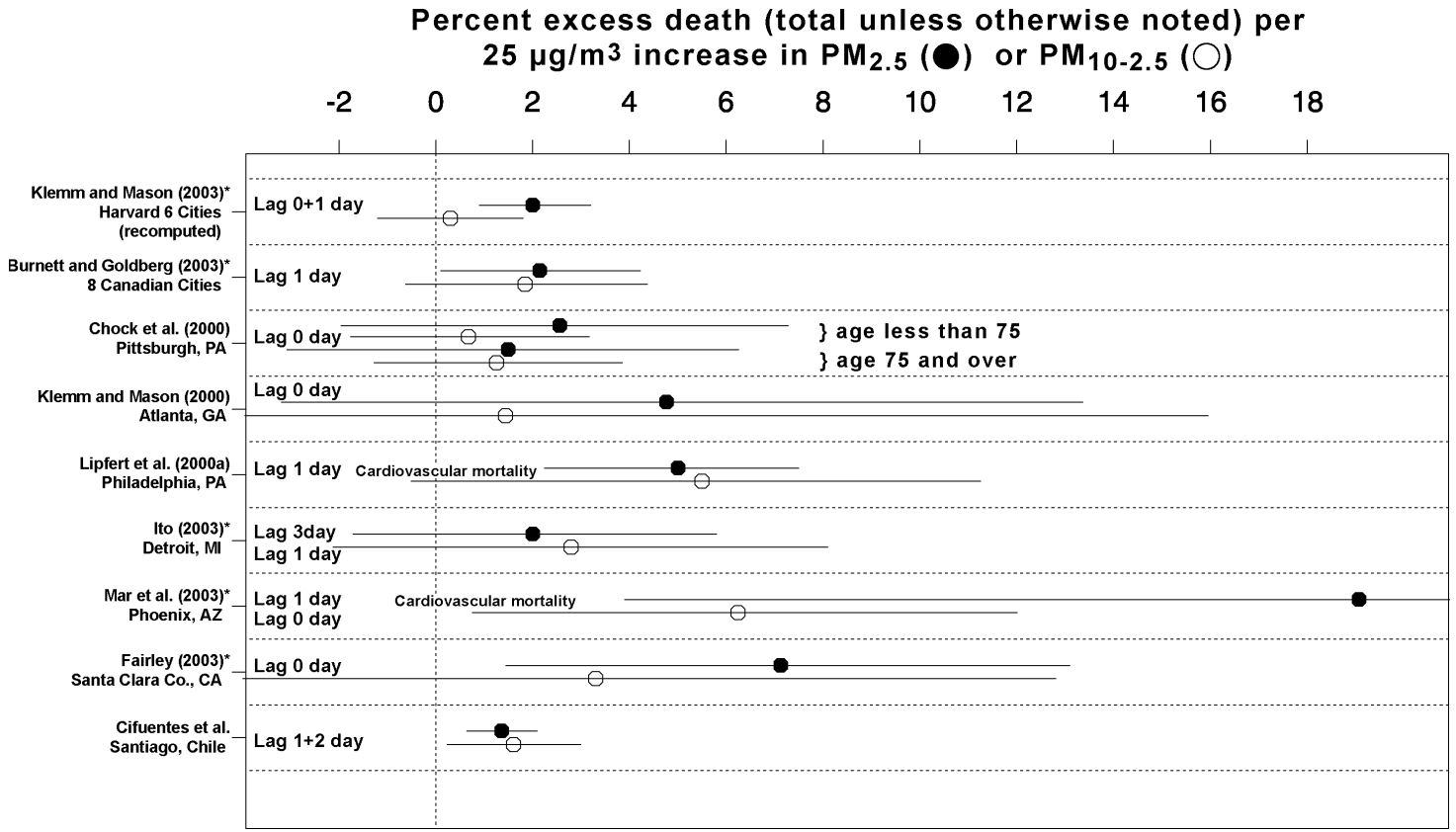

Figure 8-7. Percent excess risks estimated per 25 µg/m^3 increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10-2.5}$, based on single pollutant (PM only) models. The asterisk next to reference indicates reanalysis of data using GLM with natural splines. Other studies used GLM or OLS.

DRAFT-DO NOT QUOTE OR CITE

significant in single pollutant models. In GAM models (stringent convergence criteria) with LOESS smoothers, $PM_{2.5}$ was more significant and showed larger risk estimates than $PM_{10-2.5}$. However, in sensitivity analysis in which varying degrees of freedom for mortality temporal trends were applied in GLM models, the effect size and significance for these PM indices were often comparable. The authors commented that $PM_{10-2.5}$ coefficient was more sensitive to the extent of temporal smoothing than $PM_{2.5}$.

The Lippmann et al. (2000) results and a reanalysis (Ito, 2003) for Detroit are also noteworthy in that additional PM indices were evaluated besides those depicted in Figure 8-6, and the overall results obtained may be helpful in comparing fine- versus coarse-mode PM effects. In analyses of 1985 to 1990 data, PM-mortality relative risks and their statistical significance were generally in descending order: PM_{10}, TSP-SO_4^{-2}, and TSP-PM_{10}. For the 1992-1994 period, relative risks for equivalent distributional increment (e.g., IQR) were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for both mortality and hospital admissions categories; and SO_4^{-2} was more strongly associated with most outcomes than H^+. Consideration of the overall pattern of results led the authors to state that the mass of the smaller size index could explain a substantial portion of the variation in the larger size indices. In these data, on average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some days) and PM_{10} for 66% of TSP mass. The temporal correlation between TSP and $PM_{2.5}$ was $r = 0.63$, and that for $PM_{2.5}$ and PM_{10} was $r = 0.90$, suggesting that much of the apparent larger particle effects may well be mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger associations for sulfates than H^+, suggestive of non-acid fine particle effects, must be caveated by noting the very low H^+ levels present (often at or near non-detection limit).

Three research groups, using different methods, have examined the same Phoenix, AZ data set. While these groups used somewhat different approaches, there is some consistency among their results in that $PM_{10-2.5}$ appeared to emerge as the likely more important predictor of mortality versus $PM_{2.5}$. In the Clyde et al. (2000) analysis, PM-mortality associations were found only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the association was with $PM_{10-2.5}$, not $PM_{2.5}$. Based on the Bayes Information Criterion, the highly ranked models consistently included 1-day lagged $PM_{10-2.5}$. Smith et al. (2000) analyses found that, based on a linear PM effect, $PM_{10-2.5}$ was significantly associated with total mortality, but $PM_{2.5}$ was not. However, Smith et al.'s finding that $PM_{2.5}$ may have a threshold effect further

complicates a simple comparison of the two size-fractionated mass concentration indices. In the Mar et al. (2000 & 2003) analyses, cardiovascular mortality (CVM) was significantly associated with both $PM_{2.5}$ and $PM_{10-2.5}$. CVM was also significantly associated with a motor vehicle source category with loading of $PM_{2.5}$, EC, OC, CO, NO_2, and some trace metals, as shown by the factor analyses discussed later. The $PM_{2.5}$ in Phoenix is mostly generated from motor vehicles, whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles from natural (wind blown dust) and anthropogenic (construction and road dust) processes, and (b) organic particles from natural biogenic processes (endotoxin and molds) and anthropogenic (sewage aeration) processes. The crustal particles, however, are also likely contaminated with metals secondarily deposited over many years as the result of emissions from smelters operating until recently in the Phoenix area.

In summary, the issue regarding the relative importance of $PM_{2.5}$ and $PM_{10-.25}$ has not yet been fully resolved. Caution in interpreting size-fraction PM studies is warranted due to the problem of measurement error and the correlation between the two size fractions. Limitations of single-city studies have been noted. While the limited sample size prevented clear statistical distinction of the relative roles played by $PM_{2.5}$ and $PM_{10-.25}$, recent studies show mixed results, with some studies suggesting coarse particle effects. The relative importance may also vary depending on the chemical constituents in each size fraction, which may vary from city to city. Nevertheless, a number of studies published since the 1996 PM AQCD do appear to substantiate associations between $PM_{2.5}$ and increased total and/or CVD mortality. Consistent with the 1996 PM AQCD findings, effect-size estimates from the new studies generally fall within the range of about 2 to 6% excess total mortality per 25 $\mu g/m^3$ $PM_{2.5}$. The coarse particle ($PM_{10-2.5}$) effect-size estimates also tend to fall in the same range.

Crustal Particle Effects

Since the 1996 PM AQCD, several studies have yielded interesting new information concerning possible roles of crustal wind-blown particles or crustal particles within the fine particle fraction (i.e., $PM_{2.5}$) in contributing to observed PM-mortality effects.

Schwartz et al. (1999), for example, investigated the association of coarse particle concentrations with non-accidental deaths in Spokane, WA, where dust storms elevate coarse PM concentrations. During the 1990-1997 period, 17 dust-storm days were identified. The

PM_{10} levels during those storms averaged 263 $\mu g/m^3$, compared to 39 $\mu g/m^3$ for the entire period. The coarse particle domination of PM_{10} data on those dust-storm days was confirmed by a separate measurement of PM_{10} and $PM_{1.0}$ during a dust storm in August, 1996: the PM_{10} level was 187 $\mu g/m^3$, while $PM_{1.0}$ was only 9.5 $\mu g/m^3$. The deaths on the day of a dust storm were contrasted with deaths on control days (n = 95 days in the main analysis and 171 days in the sensitivity analysis), which are defined as the same day of the year in other years when dust storms did not occur. The relative risk for dust-storm exposure was estimated using Poisson regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity analyses considering different seasonal adjustment, year effects, and lags were conducted. The expected relative risk for these storm days with an increment of 221 $\mu g/m^3$ would be about 1.04, based on PM_{10} relative risk from past studies, but the estimated RR for high PM_{10} days was found to be only 1.00 (95% CI = 0.95-1.05) per 50 $\mu g/m^3$ PM_{10} change in this study. Schwartz et al. concluded that there was no evidence to suggest that coarse (presumably crustal) particles were associated with daily mortality.

Ostro et al. (2000 & 2003) analyzed the Coachella Valley, CA data for 1989-1998. This desert valley, where coarse particles of geologic origin comprise circa 50-60% of annual-average PM_{10} (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and Indio, CA. Cardiovascular deaths were analyzed using GAM (with stringent convergence criteria) and GLM Poisson models adjusting for temperature, humidity, day-of-week, season, and time. The actual $PM_{2.5}$ and $PM_{10-2.5}$ data were available for the last 2.5 years. Predictive models for $PM_{2.5}$ and $PM_{10-2.5}$ concentrations were developed for earlier years, but the model for $PM_{2.5}$ was not considered successful and, therefore, was not used. Thus, a strict comparison of risk estimates for $PM_{2.5}$ and $PM_{10-2.5}$ in this data set is difficult. Cardiovascular mortality was positively associated with both PM_{10} and $PM_{10-2.5}$ at multiple lags between 0 and 2 day lags; whereas $PM_{2.5}$ coefficient was positive only at lag 4 day. These results hint at crustal particle effects possibly being important in this desert situation, but the ability to discern more clearly the role of fine particles would likely be improved by analyses of more years of actual data for $PM_{2.5}$.

Laden et al. (2000) and Schwartz (2003b) analyzed Harvard Six-Cities Study data and Mar et al. (2000) analyzed the Phoenix data to investigate the influence of crustal particles in $PM_{2.5}$ samples on daily mortality. These studies are discussed in more detail in Section 8.2.2.4.3 on the

source-oriented evaluation of PM; and only the basic results regarding crustal particles are mentioned here. The elemental abundance data (from X-ray fluorescence spectroscopy analysis of daily filters) were analyzed to estimate the concentration of crustal particles in $PM_{2.5}$ using factor analysis. Then the association of mortality with fine crustal mass was estimated using Poisson regression (regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather. No positive association was found between fine crustal mass factor and mortality.

The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are not likely associated with daily mortality. However, as noted in the previous section, three analyses of Phoenix, AZ data suggested that $PM_{10-2.5}$ was associated with mortality. The results from one of the three studies (Smith et al., 2000) suggest that coarse particle mortality associations are stronger in spring and summer, when the anthropogenic portion of $PM_{10-2.5}$ is lowest as determined by factor analysis. However, during spring and summer, biogenic processes (e.g., wind-blown endotoxins and molds) may contribute more to the $PM_{10-2.5}$ fraction in the Phoenix area, clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles, per se.

Ultrafine Particle Effects

Wichmann et al. (2000) evaluated the attribution of PM effects to specific size fractions, including both the number concentration (NC) and mass concentration (MC) of particles in a given size range. To respond to the GAM convergence issues, Stolzel et al. (2003) reanalyzed the data, using GAM with stringent convergence criteria and GLM with natural splines. The study was carried out in the small German city of Erfurt (pop. 200,000) in the former German Democratic Republic. Erfurt was heavily polluted by particles and SO_2 in the 1980s, and excess mortality was attributed to high levels of TSP by Spix et al. (1993). Concentrations of PM and SO_2 have markedly dropped since then. The present study provides a much more detailed look at the health effects of ultrafine particles (diameter < 0.1 μm) than earlier studies and enables examination of effects in relation to number counts for fine and ultrafine particles, as well as in relation to their mass.

The Mobile Aerosol Spectrometer (MAS), developed by Gessellschaft für Strahlenforschung (GSF), produces number and mass concentrations in three size classes of

ultrafines (0.01 to 0.1 μm) and three size classes of larger fine particles (0.1 μm to 2.5 μm). The mass concentration $MC_{0.01\text{-}2.5}$ is well correlated with gravimetric $PM_{2.5}$, and the number concentration $NC_{0.01\text{-}2.5}$ is well correlated with total particle counts from a condensation particle counter (CPC). Mortality data were coded by cause of death, with some discrimination between underlying causes and prevalent conditions of the deceased. In the reanalysis, daily mortality data were fitted using a Poisson GAM (with stringent convergence criteria) and GLM, with adjustments for weather variables, time trends, day of week, and particle indices. Weekly data for all of Germany on influenza and similar diseases was also included in the model. In the original analysis, two types of models were fitted; one used the best single-day lag for air pollution and a second used the best polynomial distributed lag (PDL) model for air pollution. Both linear (i.e., raw) and log-transformed pollution indices were examined. PDL models in the original analysis generally had larger and more significant PM effects than single-day lag models, but the reanalysis by Stolzel et al. (2003) focused on single-day lag results only. Therefore, the numerical results in the following discussion will only include the single day lag results from the reanalysis. It should be noted that, unlike most of the recent reanalyses that have been conducted to address the GAM conversion issue, the reanalysis results from this study were virtually unchanged from the original results.

Both mass and number concentrations at the size ranges examined were mostly positively (and significantly or nearly significantly) associated with total non-accidental mortality. The best single-day lags reported were mostly 0 or 1 day lag for mass concentrations and the 4 day lag for number concentrations. For example, the estimated excess risk for $MC_{0.01\text{-}2.5}$ at lag 1 day was about 3.9% (CI = 0, 7.7) per 25 $\mu g/m^3$. The corresponding number for smaller fine particles, $MC_{0.01\text{-}1.0}$, was 3.5% (CI = −0.4, 7.7). For number concentration, the estimated excess risk for $NC_{0.01\text{-}2.5}$ at lag 4 day was about 4.1% (CI = −0.9, 9.3) per IQR (13,269 particles/cm^3). The corresponding number for smaller fine particles, $NC_{0.01\text{-}1.0}$, was 4.6% (CI = −0.3, 9.7) per IQR (12,690 particles/cm^3). An examination of the all the results for $MC_{0.01\text{-}2.5}$ and $NC_{0.01\text{-}0.1}$ shown for lags 0 through 5 days indicates that the associations were mostly positive for these mass and number concentrations, except for the "dip" around 2 or 3 day lags.

The estimated excess risks are reduced, sometimes drastically, when co-pollutants (especially SO_2 and NO_2) are included in a two-pollutant model. This is not surprising, as the number and mass concentrations of various ultrafine and fine particles in all size ranges are

rather well correlated with gaseous co-pollutants, except for the intermodal size range $MC_{1.0\text{-}2.5}$. The number correlations range from 0.44 to 0.62 with SO_2, from 0.58 to 0.66 with NO_2, and from 0.53 to 0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2, from 0.48 to 0.60 with NO_2, and from 0.56 to 0.62 with CO. The authors found that ultrafine particles, CO and NO_2 form a group of pollutants strongly identified with motor vehicle traffic. Immediate and delayed effects seemed to be independent in two-pollutant models, with single-day lags of 0 to 1 days and 4 to 5 days giving 'best fits' to data. The delayed effect of ultrafine particles was stronger than that for NO_2 or CO. The large decreases in excess risk for number concentration, particularly when NO_2 is a co-pollutant with $NC_{0.01\text{-}0.1}$, clearly involves a more complex structure than simple correlation. The large decrease in excess risk when SO_2 is a co-pollutant with $MC_{0.01\text{-}2.5}$ is not readily explained and is discussed in some detail in Wichmann et al. (2000).

SO_2 is a strong predictor of excess mortality in this study; and its estimated effect is little changed when different particle indicators are included in a two-pollutant model. The authors noted ". . .the [LOESS] smoothed dose response curve showed most of the association at the left end, below 15 $\mu g/m^3$, a level at which effects were considered biologically implausible. . ." Replacement of sulfur-rich surface coal has reduced mean SO_2 levels in Erfurt from 456 $\mu g/m^3$ in 1988 to 16.8 $\mu g/m^3$ during 1995 to 1998 and to 6 $\mu g/m^3$ in 1998. The estimated concentration-response functions for SO_2 are very different for these time periods, comparing Spix et al. (1993) versus Wichmann et al. (2000) results. Wichmann et al. concluded "These inconsistent results for SO_2 strongly suggested that SO_2 was not the causal agent but an indicator for something else." The authors offered no specific suggestions as to what the "something else" might be, but they did finally conclude that their studies from Germany strongly supported PM air pollution as being more relevant than SO_2 to observed mortality outcomes.

8.2.2.4.2 Chemical Components

Eight new studies from the U.S. and Canada examined mortality associations with specific chemical components of ambient PM. Table 8-3 shows the chemical components examined in these studies, the mean concentrations for Coefficient of Haze (CoH), sulfate, and H^+, as well as indications of those components found to be associated with increased mortality.

TABLE 8-3. NEWLY AVAILABLE STUDIES OF MORTALITY RELATIONSHIPS TO PM CHEMICAL COMPONENTS

Author, City	Mean CoH (1000ft)	Mean $SO_4^=$ (ug/m^3)	Mean H^+ (nmol/m^3)	Other PM components analyzed	Specific PM components found to be associated with mortality (comments).
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 largest Canadian cities, 1986-1996.	0.26	2.6		PM_{10}, $PM_{2.5}$, $PM_{10-.5}$, and 47 trace elements	PM_{10}, $PM_{2.5}$, CoH, sulfate, Zn, Ni, and Fe were significantly associated with total mortality in the original analysis. The reanalysis only analyzed mass concentration indices.
Fairley (1999 & 2003)*; Santa Clara County, CA.	0.5	1.8		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and nitrate	CoH, sulfate, nitrate, PM_{10}, and $PM_{2.5}$ were associated with mortality. $PM_{2.5}$ and nitrate most significant.
Goldberg et al. (2000); Goldberg and Burnett (2003); Goldberg et al. (2003)* Montreal, Quebec, Canada. 1984-1993.	0.24	3.3		Predicted $PM_{2.5}$, and extinction coefficient (visual- range derived).	CoH and extinction coefficient were associated with the deaths that were classified as having congestive heart failure before death based on medical records. Associations were stronger in warm season.
Lipfert et al., (2000a) Philadelphia, PA. 1992-1995.	0.28	5.1	8.0	Nepherometry, NH_4^+, TSP, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	Essentially all PM components were associated with mortality.
Lippmann et al. (2000); Ito (2003)* Detroit, MI. 1992-1994.		5.2	8.8	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+.
Klemm and Mason (2000) Atlanta, GA 1998-1999		5.2	8.8	Nitrate, EC, OC, oxygenated HC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	"Interim" results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were H^+, PM_{10}, and $PM_{2.5}$.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.				EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.		12.7		PM_{15}, $PM_{2.5}$, cyclohexane-solubles (CX), dichloromethane-solubles (DCM), and acetone-solubles (ACE).	PM_{15}, PM2.5, sulfate, CX, and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek et al. (2000 & 2003)* The Netherlands. 1986-1994.		3.8 (median)		PM_{10}, BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}.

*Note: The study was originally analyzed by GAM models only using default convergence criteria and at least two non-parametric smoothing terms and was recently reanalyzed by GAM using stringent convergence criteria and/or other non-GAM analyses.

Coefficient of Haze, Elemental Carbon, and Organic Carbon

CoH is highly correlated with elemental carbon (EC) and is often considered as a good PM index for motor vehicle sources, although other combustion processes such as space heating likely also contribute to CoH levels. Several studies (Table 8-3) examined CoH; and, in most cases, positive and significant associations with mortality outcomes were reported. In terms of relative significance of CoH in comparison to other PM components, CoH was not the clearly most significant PM component in most of these studies. The average level of CoH in these studies ranged from 0.24 (Montreal, Quebec) to 0.5 (Santa Clara County, CA) 1000 linear feet. The correlations between CoH and NO_2 or CO in these studies (8 largest Canadian cities; Santa Clara County, CA) were moderately high (r .0.7 to 0.8) and suggested a likely motor vehicle contribution. Both EC and OC were significant predictors of cardiovascular mortality in the Phoenix study; their effect sizes per IQR were comparable to those for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$. Also, both EC and OC represented major mass fractions of $PM_{2.5}$ (11% and 38%, respectively) and were correlated highly with $PM_{2.5}$ (r = 0.84 and 0.89, respectively). They were also highly correlated with CO and NO_2 (r = 0.8 to 0.9), indicating their associations with an "automobile" factor. Thus, the CoH and EC/OC results from the Mar et al. (2000 and 2003) study suggest that PM components from motor vehicle sources are likely associated with mortality. In a recent study in Montreal, Quebec, by Goldberg et al. (2000 and 2003), CoH appeared to be correlated with the congestive heart failure mortality (as classified based on medical records) more strongly than other PM indices such as the visual-range derived extinction coefficient (considered to be a good indicator of sulfate). However, the main focus of the study was the role of cardio-respiratory risk factors for air pollution, and the investigators warned against comparing the relative strength of associations among PM indices, pointing out complications such as likely error involved in the visual range measurements. Additionally, the estimated $PM_{2.5}$ values were predicted from other PM indices, including CoH and extinction coefficient, making it difficult to compare straightforwardly the relative importance of PM indices.

Sulfate and Hydrogen Ion

Sulfate and H^+, markers of acidic components of PM, have been hypothesized to be especially harmful components of PM (Lippmann and Thurston, 1996). The newly available studies that examined sulfate are shown in Table 8-3; two of them also analyzed H^+ data. The

sulfate concentrations ranged from 1.8 μg/m^3 (Santa Clara County, CA) to 12.7 μg/m^3(three NJ cities). Aside from the west versus east coast contrast, the higher levels observed in the three NJ cities are likely due to their study period coverage of the early 1980's, when sulfate levels were higher. Sulfate explained 25 to 30% of $PM_{2.5}$ mass in eastern U.S. and Canadian cities, but it was only 14% of $PM_{2.5}$ mass in Santa Clara County, CA. The H^+ levels measured in Detroit and Philadelphia were low. The mean H^+ concentration for Detroit, MI (the H^+ was actually measured in Windsor, a Canadian city a few miles from downtown Detroit), 8.8 nmol/m^3, was low as compared to the reported detection limit of 15.1 nmol/m^3 (Brook et al., 1997) for the measurement system used in the study. Note that the corresponding detection limit for sulfate was 3.6 nmol/m^3 (or 0.34 μg/m^3); and the mean sulfate 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 higher for sulfate than for H^+. Thus, the ambient levels and possible relative measurement errors for these data should be considered in interpreting the relative strength of mortality associations in these data.

Sulfate was a statistically significant predictor of mortality, at least in single pollutant models, in: Santa Clara County, CA; Philadelphia, PA; Newark, NJ; and Camden, NJ, but not in Elizabeth, NJ; Detroit, MI; or Montreal, CN. However, it should be noted that the relative significance across the cities is influenced by the sample size (both the daily mean death counts and number of days available), as well as the range of sulfate levels and should be interpreted with caution. Figure 8-8 shows the excess risks (± 95% CI) estimated per 5 μg/m^3 increase in 24-h sulfate reported in these studies compared to the reanalysis results of the earlier Six Cities Study result by Klemm and Mason (2003). The largest estimate was seen for Santa Clara County, CA; but the wide confidence band (possibly due to the small variance of the sulfate, because its levels were low) should be taken into account. In addition, the sulfate effect in the Santa Clara County analysis was eliminated once $PM_{2.5}$ was included in the model, perhaps being indicative of sulfate mainly serving as a surrogate for fine particles in general there. In any case, more weight should be accorded to estimates from other studies with narrower confidence bands. In the other studies, the effect size estimates mostly ranged from about 1 to 4% per 5 μg/m^3 increase in 24-h sulfate.

The relative significance of sulfate and H^+ compared to other PM components is not clear in the existing small number of publications. Because each study included different combinations of co-pollutants that had different extents of correlation with sulfate and because

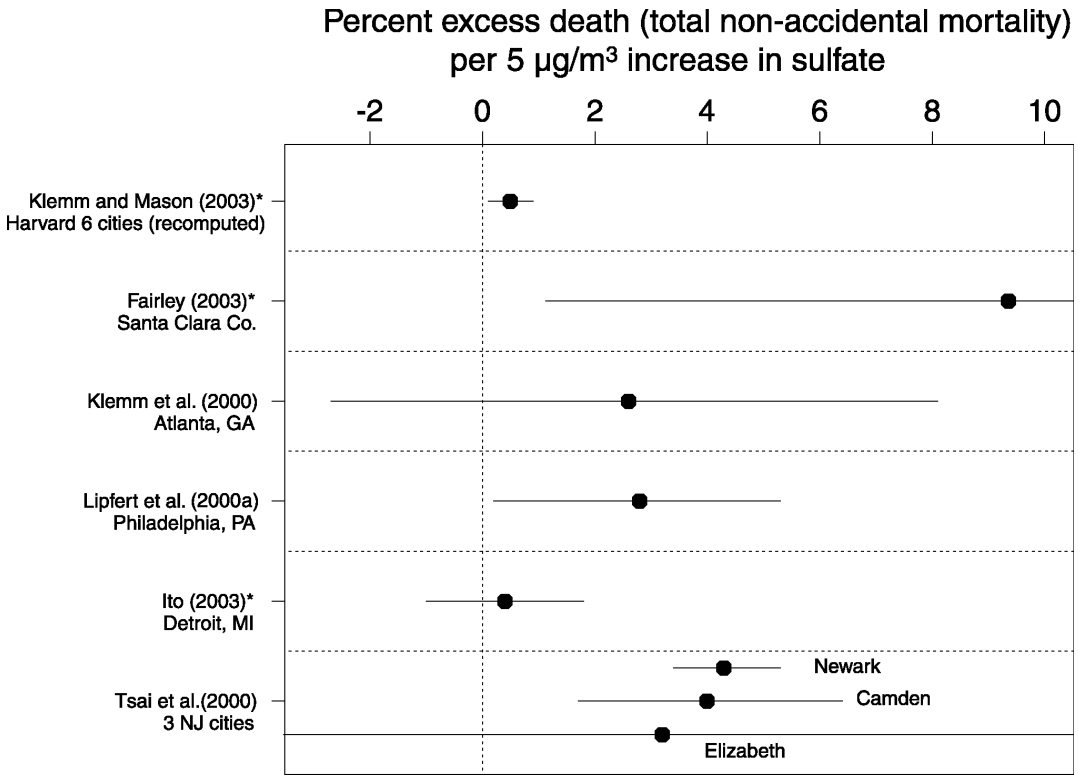

Figure 8-8. Excess risks estimated per 5 µg/m^3 increase in sulfate, based on the studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

multiple mortality outcomes were analyzed, it is difficult to assess the overall importance of sulfate across the available studies. The fact that the Lippmann et al. (2000) study and the reanalysis by Ito (2003) found that Detroit, MI data on H^+ and sulfate were less significantly associated with mortality than the size-fractionated PM mass indices may be due to acidic aerosols levels being mostly below the detection limit in that data. In this case, it appears that the Detroit PM components show mortality effects even without much acidic input.

In summary, assessment of new study results for individual chemical components of PM suggest that an array of PM components (mainly fine particle constituents) are associated with mortality outcomes, including CoH, EC, OC, sulfate, and nitrate. The variations seen with regard to the relative significance of these PM components across studies may be in part due to differences in their concentrations from locale to locale. This issue is further discussed below as part of the assessment of new studies involving source-oriented evaluation of PM components.

8.2.2.4.3 Source-Oriented Evaluations

Several new studies have conducted source-oriented evaluation of PM components. In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous co-pollutants were analyzed using factor analysis to estimate daily concentrations due to underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear combinations of associated individual variables. The mortality outcomes were then regressed on those factors (factor scores) to estimate the effect of source types rather than just individual variables. These studies differ in terms of specific objectives/focus, the size fractions from which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The main findings from these studies regarding the source-types identified (or suggested) and their associations with mortality outcomes are summarized in Table 8-4.

The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 (reanalyzed by Schwartz, 2003) aimed to identify distinct source-related fractions of $PM_{2.5}$ and to examine each fraction's association with mortality. Fifteen elements in the fine fraction samples were routinely found above their detection limits and included in the data analysis. For each of the six cities, up to 5 common factors were identified from among the 15 elements, using specific rotation factor analysis. Using the Procrustes rotation (a type of oblique rotation), the projection of the single tracer for each factor was maximized. This specification of the tracer element was based on (a) knowledge from previous source apportionment research; (b) the condition that the regression of total fine mass on that element must result in a positive coefficient; and (c) the identifications of additional local source factors that positively contributed to total fine mass regression. Three source factors were identified in all six cities: (1) a soil and crustal material factor with Si as a tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and (3) a coal combustion factor with Se as a tracer. City-specific analyses also identified a fuel combustion factor (V), a salt factor (Cl), and selected metal factors (Ni, Zn, or Mn). In the original analysis by Laden et al., a GAM Poisson regression model (with default convergence criteria), adjusting for trend/season, day-of-week, and smooth function of temperature/dewpoint, was used to estimate impacts of each source type (using absolute factor scores) simultaneously for each city. In the reanalysis reported by Schwartz (2003a), GAM models with LOESS smoothers were replaced with penalized splines. Summary estimates across cities were obtained by combining the city-specific estimates, using inverse-variance weights. The identified factors and their

TABLE 8-4. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PM COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality (Comments)
Laden et al., (2000); Schwartz (2003)* Harvard Six Cities. 1979-1988.	*Soil and crustal material*: Si *Motor vehicle emissions:* Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality was associated with the mobile source factor. Coal combustion factor was also positively associated with mortality. Crustal factor from fine particles not associated (negative but not significant) with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust:* Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and K_S (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S	*$PM_{2.5}$ factors results:* Motor vehicle factor (1 day lag), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were significantly positively associated with cardiovascular mortality.
	$PM_{10-2.5}$ (from dichot) trace elements: *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	Factors from dichot $PM_{10-2.5}$ trace elements not analyzed for their associations with mortality because of the small sample size (every 3rd-day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions:* Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.
Ozkaynak 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.

*Note: The study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms, but was later reanalyzed using more stringent convergence criteria and/or other approaches.

tracers are listed in Table 8-4. The reanalysis using penalized splines changed somewhat the risk estimates for source-apportioned mass concentrations in each city compared to those in the original GAM results (increasing estimates in some cities and reducing them in others), but the combined estimates across the six cities did not change substantially. The combined estimates

indicated that the largest increase in daily mortality was associated with the mobile source associated fine mass concentrations, with an excess death risk increase of 9.3% (95% CI: 4.0, 14.9) per 25 $\mu g/m^3$ source-apportioned $PM_{2.5}$ (average of 0 and 1 day lags). The corresponding value for the $PM_{2.5}$ mass apportioned for the coal combustion factor was 2.0% (95% CI: –0.3, 4.4). The crustal factor was not associated with mortality (-5.1%; 95% CI = –13.9, 4.6).

Mar et al. (2000) analyzed PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$ measured by two methods, and various sub-components of $PM_{2.5}$ for their associations with total (non-accidental) and cardiovascular deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor analysis-derived factor scores. In the original analysis, GAM Poisson models (with default convergence criteria) were used and adjusted for season, temperature, and relative humidity. In the reanalysis (Mar et al., 2003), GAM models with stringent convergence criteria and GLM models with natural splines were used. Only cardiovascular mortality was analyzed in the reanalysis; and the results for that category are summarized here. The evaluated air pollution variables included O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. A factor analysis conducted on the chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC) identified factors for motor vehicle emissions/re-suspended road dust; soil; vegetative burning; local SO_2 sources; and regional sulfate (see Table 8-4). The results of mortality regression with these factors suggested that the motor vehicle factor (lag 1 day), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were each had significant positive associations with cardiovascular mortality. The $PM_{2.5}$ mass was not apportioned to these factors in this study; so information on the excess-deaths estimate per source-apportioned $PM_{2.5}$ concentrations were not available. The authors also analyzed elements from dichot $PM_{10-2.5}$ samples and identified soil, a source of coarse fraction metals (industry), and marine influence factors. However, these factors were not analyzed for their associations with mortality outcomes due to the short measurement period (starting in June 1996 with every 3rd-day sampling).

It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included factor analysis on the elements from the coarse fraction and identified essentially the same factors ("a source of coarse fraction metals" factor in Mar et al.'s study was called "the anthropogenic elements" in Smith et al.'s study). While Smith et al. did not relate these factors

to mortality (due to a small sample size), they did show that the anthropogenic elements were low in summer and spring, when the $PM_{10-2.5}$ effect was largest. These results suggest that the $PM_{10-2.5}$ effects may not necessarily be due to anthropogenic components of the coarse particles, the biogenically-generated coarse particles perhaps being key during the warmer months (as noted earlier).

Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis - Poisson regression techniques. During the three-year study period (1981-1983), extensive chemical speciation data were available, including nine trace elements, sulfate, and particulate organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory mortality were analyzed. A factor analysis of trace elements and sulfate was first conducted and identified several major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson regression of mortality on these factors, an alternative approach was also used, in which the inhalable particle mass (IPM, $D_{50} < 15$ μm) was first regressed on the factor scores of each of the source types to apportion the PM mass and then the estimated daily PM mass for each source type was included in Poisson regression, so that RR could be calculated per mass concentration basis for each PM source type. Oil burning (V, Ni), various industrial sources (Zn, Cd), motor vehicle (Pb, CO), and secondary aerosols, as well as the individual PM indices IPM, FPM ($D_{50} < 3.5$ μm), and sulfates, were all associated with total and/or cardiorespiratory mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were higher (1.10) than those for individual PM indices (1.02).

Özkaynak et al. (1996) had earlier analyzed 21 years of mortality and air pollution data for Toronto, Canada. In addition to the usual simultaneous inclusion of multiple pollutants in mortality regressions, they also conducted a factor analysis of all the air pollution and weather variables, including TSP, SO_2, CoH, NO_2, O_3, CO, relative humidity and temperature. The factor with the largest variance contribution (50%) had the highest factor loadings for CO, CoH, and NO_2 and was considered by them to be representative of motor vehicle emissions, since this pollution grouping was also consistent with the emission inventory information for that city. After filtering out seasonal cycles and adjusting for temperature and day-of-week effects, they then regressed mortality on the factor scores (a linear combination of standardized scores for the

covariates). The estimated effects of motor vehicle pollution on mortality ranged from 1 to 6% for different specific health outcomes.

In summary, these source-oriented factor analyses studies suggest that a number of source types are associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with mortality in the Harvard Six Cities data. In Phoenix, where coarse particles were reported to be associated with mortality, the associations between the factors related to coarse particles (soil, marine influence, and anthropogenic elements) and mortality could not be evaluated due to the small sample size. Thus, although some unresolved issues remain (mainly due to the lack of sufficient data), the limited results from the source-oriented evaluation approach (using factor analysis) thus far seem to implicate fine particles of anthropogenic origin as being most important (versus crustal particles of geologic origin) in contributing to increased mortality risks.

8.2.2.5 New Assessments of Cause-Specific Mortality

Consistent with similar findings described in the 1996 PM AQCD, most of the newly available studies summarized in Tables 8-1 and 8A-1 that examined non-accidental total, circulatory, and respiratory mortality categories (e.g., Samet et al., 2000a,b and the reanalysis by Dominici et al., 2002 and 2003) found significant PM associations with both cardiovascular and/or respiratory-cause mortality. Several studies (e.g., Fairley, 1999), his reanalysis, 2003; Wordley et al., 1997; Prescott et al., 1998) reported estimated PM effects that were generally higher for respiratory deaths than for circulatory or total deaths. Once again, the NMMAPS results for U.S. cities are among those of particular note here due to the large study size and the combined, pooled estimates derived for various U.S. regions.

The NMMAPS 90-cities analyses not only examined all-cause mortality (excluding accidents), but also evaluated cardio-respiratory and other remaining causes of deaths. Results were presented for all-cause, cardio-respiratory, and "other" mortality for lag 0, 1, and 2 days. The investigators commented that, compared to the result for cardio-respiratory deaths showing 1.6% (CI = 0.8, 2.4) increase per 50 $\mu g/m^3 PM_{10}$ in a GLM model (versus 1.1% for total non-accidental mortality using GLM), there was less evidence for non-cardio-respiratory deaths. However, the estimates for "other" mortality, though less than half those for cardio-respiratory mortality, were nevertheless positive, with a fairly high posterior probability (e.g., 0.92 at lag 1

day) that the overall effects were greater than zero. It should be noted that the "other" (other than cardio-respiratory) underlying cause of mortality may include deaths that had contributing cardiovascular or respiratory causes. For example, Lippmann et al. (2000) noted that the "other" (non-circulatory and non-respiratory) mortality showed seasonal cycles and apparent influenza peaks, suggesting that this series may have also been influenced by respiratory contributing causes. Thus, interpretation of the observed associations between PM and broad "specific" categories of underlying causes of death may not be straightforward.

Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-specific mortality across a broad range of lag times (0-5 days) in Cook Co., IL; Los Angeles Co., CA; and Maricopa Co., AZ. Total non-accidental mortality, as well as deaths related to cardiovascular disease (CVD), cerebrovascular disease (CRV), and chronic obstructive lung disease (COPD) were analyzed in the original study. The data for Cook Co. and Maricopa Co. were reanalyzed using GAM model with stringent convergence criteria and GLM model with natural splines (Moolgavkar, 2003). Cerebrovascular disease mortality was not reanalyzed because there was little evidence of association for PM with this category at any lag in any of the three counties analyzed. Moolgavkar reported that varying patterns of results were obtained for PM indices in evaluations of daily deaths related to CVD and COPD in the two counties. In the Cook Co. (Chicago) area, the association of PM_{10} with CVD mortality was statistically significant at a lag of 3 days based on a single-pollutant analysis and remained significantly associated with CVD deaths with a 3-day lag in two pollutant models including one or another of CO, NO_2, SO_2, or O_3. In Los Angeles single-pollutant analyses, CVD mortality was significantly associated with PM_{10} (2 day lag) and $PM_{2.5}$ (0 and 1 day lag). Their percent excess risk estimates were up to twice those for total non-accidental mortality. In a two-pollutant model with CO (most strongly positively associated with mortality in Los Angeles Co. among the pollutants), PM_{10} risk estimates were reduced. However, $PM_{2.5}$ excess risk estimates in the two-pollutant model with CO nearly doubled (2.5% per 25$\mu g/m^3$ increase in $PM_{2.5}$ to 4.8% using GLM); whereas that for CO became significantly negative. Obviously, CO and $PM_{2.5}$ were correlated ($r \approx 0.58$), and the estimated associations were likely confounded between these two pollutants in this locale. With regard to COPD deaths, PM_{10} was significantly associated with COPD mortality (lag 2 days) in Cook Co., but in Los Angeles Co., both PM_{10} and (especially) $PM_{2.5}$ showed erratic associations with COPD mortality at varying lags, alternating positive and

negative (significantly, at lag 3 day) coefficients. The combination of the every 6th-day PM data in Los Angeles (versus daily PM_{10} in Cook Co.) and relatively small daily counts for COPD (median = 6/day versus 57/day for CVD) makes the effective sample size of COPD mortality analysis small and the results unstable.

Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the 12 APHEA European cities (APHEA1). Using Poisson autoregressive models parametrically adjusting for trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated for each city and "meta-analyses" of city-specific estimates were conducted. The pooled excess risk estimates for cardiovascular mortality were 1.0% (0.3, 1.7) per 25 $\mu g/m^3$increase in BS and 2.0% (0.5, 3.0) per 50 $\mu g/m^3$increase in SO_2 in western European cities. The pooled risk estimates for respiratory mortality in the same cities were 2.0% (0.8, 3.2) and 2.5% (1.5, 3.4) for BS and SO_2, respectively.

Seeking unique cause-specificity of effects associated with various pollutants has been difficult because the "cause specific" categories examined are typically rather broad (usually cardiovascular and respiratory) and overlap and because cardiovascular and respiratory conditions tend to occur together. Examinations of more specific cardiovascular and respiratory subcategories may be necessary to test hypotheses about any specific mechanisms, but smaller sample sizes for more specific sub-categories may make a meaningful analysis difficult. The Hoek et al. (2000 and 2001) study and its reanalysis by Hoek (2003) took advantage of a larger sample size to examine cause-specific mortality. The large sample size, including the whole population of the Netherlands (mean daily total deaths ~330, or more than twice that of Los Angeles County), allowed examination of specific cardiovascular causes of deaths. The reanalysis using GAM with stringent convergence criteria as well as GLM with natural splines either did not change or even increased the effect estimates. Deaths due to heart failure, arrhythmia, and cerebrovascular causes were more strongly (~2 to 4 times larger excess risks) associated with air pollution than the overall cardiovascular deaths. The investigators concluded that specific cardiovascular causes (such as heart failure) were more strongly associated with air pollution than total cardiovascular mortality, but noted that the largest contribution to the association between air pollution and cardiovascular mortality was from ischemic heart disease (about half of all CVD deaths). The analyses of specific respiratory causes, COPD, and pneumonia yielded even larger risk estimates (e.g., ~ 6 to 10 times, respectively, larger than that

for overall cardiovascular deaths). Estimated PM_{10} excess risks per 50 $\mu g/m^3$ PM_{10} (average of 0 through 6 day lags) were 1.2% (0.2, 2.3), 0.9% (−0.8, 2.7), 2.7% (−4.2, 10.1), 2.4% (−2.3, 7.4), 6.1% (1, 11.4), and 10.3% (3.7, 17.2), respectively, for total non-accidental, cardiovascular, arrhythmia, heart failure, COPD, and pneumonia, using GAM models with stringent convergence criteria. Thus, the results from this study with a large effective sample size also confirm past observations that PM risk estimates for specific causes of cardiovascular or respiratory mortality can be larger than those estimated for total non-accidental mortality.

As mentioned earlier in the multi-cities results section, Schwartz (2003) reanalyzed data from Braga et al. (2001) to examine the lag structure of PM_{10} associations with specific causes of mortality in ten U.S. cities. The pattern of larger PM_{10} excess risk estimates for respiratory categories than for cardiovascular categories found in this study was similar to that in the Hoek et al. analyses noted above. For example, the combined risk estimates across 10 cities per 50 $\mu g/m^3$ increase in PM_{10} (2-day mean) were 4.1% (2.5, 5.6), 7.7% (4.1, 11.5), and 11.0% (7, 15.1) for cardiovascular, COPD, and pneumonia, respectively, using GAM with stringent convergence criteria. These values were even larger for unconstrained distributed lag models.

The Goldberg et al. (2000) study, and its reanalyses (Goldberg et al., 2003; Goldberg and Burnett, 2003) in Montreal, CN, investigated the role of co-morbidity prior to deaths in PM-mortality associations for various subcategories, including cancer, acute lower respiratory disease, chronic coronary artery disease, and congestive heart failure (CHF). They could classify deaths into these subcategories using medical records from the universal Quebec Health Insurance Plan (QHIP). This way of classifying deaths would presumably take into account more detailed information on the disease condition prior to death than the "underlying cause" in the death records. Thus, the PM-mortality associations could be compared by using subcategories classified from death records versus those classified from QHIP medical records. The Goldberg and Burnett (2003) reanalysis found that total non-accidental mortality (which was significantly associated with PM indices in the original report using GAM with default convergence criteria) was not associated with PM indices in GLM models. They reported that the associations between PM and non-accidental mortality were rather sensitive to weather model specification and did not find significant PM associations with most of the subcategories as defined from either QHIP or underlying cause. However, they did find significant associations between CoH, NO_2, and SO_2 and the CHF deaths as defined from QHIP, but not the

CHF deaths as defined from underlying cause. The association was even stronger in warm seasons. It should be noted, however, that while the period for this study was relatively long (~10 years) and the counts for the total non-accidental deaths were not small (median = 36 deaths per day), the counts for various subcategories were quite small (e.g., CHF underlying cause mortality mean = 0.75 per day).

A recent study (Gouveia and Fletcher, 2000), using data from Sao Paulo, Brazil, 1991-1993, examined child mortality (age under 5 years). The Poisson auto-regressive model included parametric terms (e.g., quadratic, two-piece linear temperature etc.) to adjust for weather and temporal trends. Although Gouveia and Fletcher found significant associations between air pollution and elderly mortality, they did not find statistically significant associations between air pollution and child respiratory mortality (the PM_{10} coefficient was negative and not significant). However, it should be noted that the average daily respiratory mortality counts for this study were relatively small (~2.4/day). With the modest length of observations (3 years), the statistical power of the data was likely less than desirable, and there may not have been sufficient power to elucidate the range of short-term PM effects on child respiratory mortality. Again, evaluation of the role of varying contributing conditions to PM-mortality associations are often challenged by the sample size problem.

Overall, then, the above assessment of newly available studies provides interesting additional new information with regard to cause-specific mortality related to ambient PM. That is, a growing number of studies continue to report increased cardiovascular- and respiratory-related mortality risks as being significantly associated with ambient PM measures at one or another varying lag times. When specific subcategories of cardiovascular disease were examined in a large population (The Netherlands study by Hoek et al.), some of the subcategories such as heart failure were more strongly associated with PM and other pollutants than total cardiovascular mortality. Largest effect estimates are most usually reported for 0-1 day lags (with some studies also now noting a second peak at 3-4 day lags). A few of the newer studies also report associations of PM metrics with "other" (i.e., non-cardiorespiratory) causes, as well. However, at least some of these "other" associations may also be due to seasonal cycles that include relationships to peaks in influenza epidemics that may imply respiratory complications as a contributing cause to the "other" deaths. Alternately, the "other" category may include sufficient numbers of deaths due to diabetes or other diseases which may also

involve cardiovascular complications as contributing causes. Varying degrees of robustness of PM effects are seen in the newer studies, as typified by PM estimates in multiple pollutant models containing gaseous co-pollutants. That is, some studies show little effect of gaseous pollutant inclusion on estimated PM effect sizes, some show larger reductions in PM effects to non-significant levels upon such inclusion, and a number also report significant associations of cardiovascular and respiratory effects with one or more gaseous co-pollutants. Thus, the newer studies both further substantiate PM effects on cardiovascular- and respiratory-related mortality, while also pointing toward possible significant contributions of gaseous pollutants to such cause-specific mortality. The magnitudes of the PM effect size estimates are consistent with the range of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

8.2.2.6 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality

The most salient key points to be extracted from the above discussion of newly available information on short-term PM exposures relationships to mortality can be summarized as follow:

PM_{10} effects estimates. Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality analyses published. Estimated mortality relative risks in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. However, due to the concerns regarding the GAM convergence issue, quantitative evaluations were made here based only on the studies that either did not use GAM Poisson model with default convergence criteria or on those studies that have reanalyzed the data using more stringent convergence criteria and/or used fully parametric approaches. Of particular importance are several studies which evaluated multiple cities using consistent data analytical approaches. The NMMAPS analyses for the largest 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2002 and 2003), derived a combined nationwide excess risk estimate of about 1.4% (1.1% using GLM) increase in total (non-accidental) mortality per 50 $\mu g/m^3$increase in PM_{10}. Other well-conducted multi-city analyses, as well as various single city analyses, obtained larger PM_{10}-effect size estimates for total non-accidental mortality, generally falling in the range of 2 to 3.5% per 50 $\mu g/m^3$increase in PM_{10}. This is consistent with, but somewhat lower than, the range of PM_{10} risk estimates given in the 1996 PM AQCD. However, somewhat more geographic heterogeneity is evident among the newer multi-city study results than was the case among the fewer studies assessed in the 1996 PM AQCD. In the NMMAPS analysis of the 90

largest U.S. cities data, for example, the risk estimates varied by U.S. geographic region, with the estimate for the Northeast being the largest (approximately twice the nation-wide estimates). The observed heterogeneity in the estimated PM risks across cities/regions could not be explained by city-specific explanatory variables, such as mean levels of pollution and weather, mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error. Notable apparent heterogeneity was also seen among effects estimates for PM (and SO_2) indices in the multi-city APHEA studies conducted in European cities. In APHEA2, they found that several city-specific characteristics, such as NO_2 levels and warm climate, were important effect modifiers. The issue of heterogeneity of effect estimates is discussed further in Section 8.4.

Model specification Issue: The investigations of the GAM convergence issue also led to examination of the sensitivity of the PM risk estimates to different model specifications. Several reanalyses examined the sensitivity of results to varying the degrees of freedom for smoothing of weather and temporal trends. PM risk estimates were often reduced when more degrees of freedom were given to model temporal trends. While what constitutes an "adequate" extent of smoothing (from an epidemiologic viewpoint) is currently not known, the overall assessment of PM risk estimates should take into consideration the range of sensitivity of results to this aspect of model specification.

*Confounding and effect modification by other pollutant*s. Numerous new short-term PM exposure studies not only continue to report significant associations between various PM indices and mortality, but also between gaseous pollutants (O_3, SO_2, NO_2, and CO) and mortality. In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models did not meaningfully affect the PM-effect size estimates. This was the case for the NMMAPS 90 cities study with regard to the overall combined U.S. regional and nationwide risk estimates derived for that study. The issue of confounding is discussed further in Section 8.4.

*Fine and coarse particle effect*s. Newly available studies provide generally positive (and often statistically significant) $PM_{2.5}$ associations with mortality, with effect size estimates falling in the range reported in the 1996 PM AQCD. New results from Germany appear to implicate both ultrafine (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as being important contributors to increased mortality risks. As to the relative importance of fine and coarse particles, in the 1996 PM AQCD there was only one acute mortality study (Schwartz

et al., 1996a) that examined this issue. The results of that study of six U.S. cities suggested that fine particles ($PM_{2.5}$), were associated with daily mortality, but not coarse particles ($PM_{10-2.5}$), except for in Steubenville, OH.. Now, eight studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality. While the results from some of these new studies (e.g., the Santa Clara County, CA analysis [Fairley, 1999]) did suggest that $PM_{2.5}$ was more important than $PM_{10-2.5}$ in predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses [Clyde et al., 2000; Mar et al., 2000; Smith et al., 2000]) suggest that $PM_{10-2.5}$ may also be important in at least some locations. Seasonal dependence of size-related PM component effects observed in some of the studies complicates interpretations.

Chemical components of PM. Several new studies have examined the role of specific chemical components of PM. The studies conducted in U.S., Canadian, and European cities showed mortality associations with specific fine particle components of PM, including sulfate, nitrate, and CoH; but their relative importance varied from city to city, likely depending on their levels (e.g., no clear associations in those cities where H^+ and sulfate levels were very low, i.e., circa non-detection limits). The results of several studies that investigated the role of crustal particles, although somewhat mixed, overall do not appear to support associations between crustal particles and mortality (see also the discussion of source-oriented evaluations presented below).

*Source-oriented evaluation*s. Several studies conducted source-oriented evaluations of PM components using factor analysis. The results from these studies generally indicated that several combustion-related source-types are likely associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with total non-accidental mortality in the Harvard Six Cities data, and the soil (i.e., crustal) factor from fine particles in the Phoenix data was not associated with cardiovascular mortality. Thus, the source-oriented evaluations seem to implicate fine particles of anthropogenic origin as being most important in contributing to increased mortality, but generally do not support increased mortality risks being related to short-term exposures to crustal materials in U.S. ambient environments.

Cause-specific mortality. Findings for new results concerning cause-specific mortality comport well with those for total (non-accidental) mortality, the former showing generally larger effect size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess

risks than for total mortality risks. An analysis of specific cardiovascular causes in a large population (The Netherlands) suggested that specific causes of deaths (such as heart failure) were more strongly associated with PM (and other pollutants) than total cardiovascular mortality.

Lags. In general, maximum effect sizes for total mortality appear to be obtained with 0-1 day lags, with some studies indicating a second peak for 3-4 days lags. There is also some evidence that, if effects distributed over multiple lag days are considered, the effect size may be larger than for any single maximum-effect-size lag day. Lags are discussed further in Section 8.4.

Threshold. Few new short-term mortality studies explicitly address the issue of thresholds. One study that analyzed Phoenix, AZ data (Smith et al., 2000) did report some limited evidence suggestive of a possible threshold for $PM_{2.5}$. However, several different analyses of larger PM_{10} data sets across multiple cities (Dominici, et al., 2002; Daniels et al., 2000; and reanalysis by Dominici et al., 2003) generally provide little or no support to indicate a threshold for PM_{10} mortality effects. Threshold issues are discussed further in Section 8.4.

8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter

8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document

8.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies

Mortality effects associated with chronic, long-term exposure to ambient PM have been evaluated in cross-sectional studies and, more recently, in prospective cohort studies. A number of older cross-sectional studies from the 1970s provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM, especially with respect to fine mass or sulfate (SO_4^{-2}) concentrations. However, questions unresolved at that time regarding the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) on such purely "ecological" studies or on quantitative estimates of PM effects derived from them. Evidence comparing the toxicities of specific PM components was relatively limited, although the sulfate and acid components were discussed in detail in the 1986 PM AQCD (U.S. Environmental Protection Agency, 1986).

8.2.3.1.2 Semi-Individual (Prospective Cohort) Chronic Exposure Studies

Prospective cohort, semi-individual studies of mortality associated with chronic exposures to air pollution of outdoor origins have yielded especially valuable insights into the adverse health effects of long-term PM exposures. Such semi-individual cohort studies using subject-specific information about relevant covariates (such as cigarette smoking, occupation, etc.) typically are capable of providing more certain findings of long-term PM exposure effects than are purely "ecological studies" (Künzli and Tager, 1997). The new, better designed cohort studies, as discussed below, have largely confirmed the magnitude of PM effect estimates derived from past cross-sectional studies.

The extensive Harvard Six-Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS study did not evaluate the possible contributions of other air pollutants. Neither study considered multi-pollutant models, although the Six-City study did examine various PM and gaseous pollutant indices (including total particles, $PM_{2.5}$, SO_4^{-2}, H^+, SO_2, and ozone), and found that sulfate and $PM_{2.5}$ fine particles were most strongly associated with mortality. The excess RR estimates originally reported for total mortality in the Six-Cities study (and 95 percent confidence intervals, CI) per increments in PM indicator levels were: Excess RR = 18% (CI = 6.8%, 32%) for 20 $\mu g/m^3$ PM_{10}; excess RR = 13.0% (CI = 4.2%, 23%) for 10 $\mu g/m^3$ $PM_{2.5}$; and excess RR = 13.4% (CI = 5.1%, 29%) for 5 $\mu g/m^3$ SO_4^{-2}. The estimates for total mortality derived from the ACS study were excess RR = 6.6% (CI = 3.5%, 9.8%) for 10 $\mu g/m^3$ $PM_{2.5}$ and excess RR 3.5% (CI = 1.9%, 5.1%) for 5 $\mu g/m^3$ SO_4^{-2}. The ACS pollutant RR estimates were smaller than those from the Six-Cities study, although their 95% confidence intervals overlap. In some cases in these studies, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in cities with historically higher PM levels (e.g., Steubenville, OH); but more current PM measurements were used to estimate the chronic PM exposures. In the ACS study, the pollutant exposure estimates were based on concentrations at the start of the study (during 1979-1983). In addition, the average age of the ACS cohort was 56, which could overestimate the pollutant RR estimates and perhaps underestimate the life-shortening associated with PM associated mortality. Still, although caution must be exercised regarding use of the reported quantitative risk estimates, the Six-Cities and ACS semi-individual studies

provided consistent evidence of significant mortality associations with long-term exposure to ambient PM.

In contrast to the Six-Cities and ACS studies, early results reported by Abbey et al. (1991) and Abbey et al. (1995a) from another prospective cohort study, the Adventist Health Study on Smog (AHSMOG), found no significant mortality effects of previous PM exposure in a relatively young cohort of California nonsmokers. However, these analyses used TSP as the PM exposure metric, rather than more health-relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study, and considered a shorter follow-up time than the Six-Cities study (ten years versus 15 years for the Six-Cities study). Further, the AHSMOG study included only nonsmokers (indicated by the Six-Cities Study as having lower pollutant RR's than smokers), suggesting that a longer follow-up time than considered in the past (10 years) might be required to have sufficient power to detect significant pollution effects than would be needed in studies that include smokers (such as the Six-Cities and ACS studies). Thus, greater emphasis was placed in the 1996 PM AQCD on the results of the Six-Cities and ACS studies.

Overall, the previously available chronic PM exposure studies collectively indicated that increases in mortality are associated with long-term exposure to ambient airborne particles; and effect size estimates for total mortality associated with chronic PM exposure indices appeared to be much larger than those reported from daily mortality PM studies. This suggested that a major fraction of the reported mortality relative risk estimates associated with chronic PM exposure likely reflects cumulative PM effects above and beyond those exerted by the sum of acute exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM AQCD (Chapter 12) reached several conclusions concerning four key questions about the prospective cohort studies, as noted below:

(1) Have potentially important confounding variables been omitted?

"While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as individual and community risk factors are included in the analyses." These include individual variables such as education, occupational exposure to dust and fumes, and physical activity, as well as ecological

(community) variables such as regional location, migration, and income distribution. Further refinement of the effects of smoking status may also prove useful."

(2) Can the most important pollutant species be identified?

"The issue of confounding with co-pollutants has not been resolved for the prospective cohort studies . . . Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies." The ability to separate the effects of different pollutants, each measured as a long-term average on a community basis, was clearly most limited in the Six Cities study. The ACS study offered a much larger number of cities, but did not examine differences attributable to the spatial and temporal differences in the mix of particles and gaseous pollutants across the cities. The AHSMOG study constructed time- and location-dependent pollution metrics for most of its participants that might have allowed such analyses, but no results were reported.

(3) Can the time scales for long-term exposure effects be evaluated?

"Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. This potential was greater in the Six Cities and AHSMOG studies because of the greater length of the historical air pollution data for the cohort [and the availability of air pollution data throughout the study]. The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure."

(4) Is it possible to identify pollutant thresholds that might be helpful in health assessments?

"Model specification searches for thresholds have not been reported for prospective cohort studies. . . . Measurement error in pollution variables also complicates the search for potential threshold effects. . . . The problems that complicate threshold detection in the population-based studies have a somewhat different character for the long-term studies."

8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures

Considerable further progress has been made towards addressing the above issues. As an example, extensive reanalyses (Krewski et al., 2000) of the Six-Cities and ACS Studies (sponsored by HEI), indicate that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses. The HEI reanalysis project demonstrated that small corrections in input data have very little effect on the findings and that alternative model specifications further substantiate the robustness of the originally reported findings. In addition, some of the above key questions have been further investigated by Krewski et al. (2000) via sensitivity analyses (in effect, new analyses) for the Six City and ACS studies data sets, including consideration of a much wider range of confounding variables. Newly published analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiate original findings and also provide much clearer, stronger evidence for ambient PM exposure relationships with increased lung cancer risk. Newer published analyses of AHSMOG data (Abbey et al., 1999; Beeson et al., 1998) also extend the ASHMOG findings and show some analytic outcomes different from earlier analyses reported out from the study. Results from the Veterans' Administration- Washington University (hereafter called "VA") prospective cohort study are also now available (Lipfert et al., 2000b). Other additional, new studies suggestive of possible effects of sub-chronic PM exposures on fetal and infant development/mortality (Woodruff et al., 1997; Bobak and Leon, 1998; Lipfert, 2000; Chen et al., 2002) are also discussed below.

8.2.3.2.1 Health Effects Institute Reanalyses of the Six-Cities and ACS Studies

The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) Studies of air pollution and mortality. The following description of approach, key results, and conclusions is largely extracted from the Executive Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort was approached in two steps:

- Part I: Replication and Validation. The Reanalysis Team sought to test (a) whether the original studies could be replicated via a quality assurance audit of a sample of the original data and (b) whether the original numeric results could be validated.
- Part II: Sensitivity Analyses. The Reanalysis Team tested the robustness of the original analyses to alternate risk models and analytic approaches.

The Part I audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed that data were of generally high quality with few exceptions. In both studies, a few errors were found in the data coding for and exclusion of certain subjects; but when those subjects were included in the analyses, they did not materially change the results from those originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses in Part II.

The Reanalysis Team was able to replicate the original results for both studies using the same data and statistical methods as used by the original investigators, as shown in Table 8-5. The Reanalysis Team confirmed the original point estimates. For the Six Cities Study, they reported the excess relative risk of mortality from all causes associated with an increase in fine particles of 10 $\mu g/m^3$ to be 14%, close to the 13% reported by the original investigators. For the ACS Study, they reported the relative risk of all-cause mortality associated with a 10 $\mu g/m^3$ increase in fine particles to be 7.0% in the reanalysis, close to the original 6.6% value.

The Part II sensitivity analysis applied an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions and model specifications. The Reanalysis Team first applied the standard Cox model used by the original investigators and included variables in the model for which data were available from both original studies, but had not been used in the published analyses (e.g., physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.

Next, for both the Six Cities and ACS Studies, the Reanalysis Team investigated the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. These analyses did not find differences in PM-mortality associations among subgroups based on various personal characteristics (e.g., including gender, smoking status,

TABLE 8-5. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM[a]	
Original Investigators' Findings		Total Mortality Excess Relative Risk (95% CI)	Cardiopulmonary Mortality Excess Relative Risk (95% CI)
Six City[b]	$PM_{2.5}$	13% (4.2%, 23%)	18% (6.0%, 32%)
Six City[b]	$PM_{15/10}$	18% (6.8%, 32%)	e
ACS Study[c]	$PM_{2.5}$	6.6% (3.5%, 9.8%)	12% (6.7%, 17%)
HEI reanalysis Phase I: Replication			
Six City Reanalysis[d]	$PM_{2.5}$	14% (5.4%, 23%)	19% (6.5%, 33%)
	PM_{15}	19% (6.1%, 34%)	20% (2.9%, 41%)
ACS Study Reanalysis[d]	$PM_{2.5}$	7.0% (3.9%, 10%)	12% (7.4%, 17%)
	PM_{15} (dichot)	4.1% (0.9%, 7.4%)	7.3% (3.0%, 12%)
	PM_{15} (SSI)	1.6% (−0.8%, 4.1%)	5.7% (2.5%, 9.0%)

[a]Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, scaled to increments of 20 $\mu g/m^3$ 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]Results presented only by smoking category subgroup.

exposure to occupational dusts and fumes, and marital status). However, estimated effects of fine particles did vary with educational level: the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those with more education. The Reanalysis Team postulated that this finding could be attributable to some unidentified socioeconomic effect modifier. The authors concluded "The Reanalysis Team found little evidence that questionnaire variables had led to confounding in either study, thereby strengthening the conclusion that the observed association between fine particle air pollution and mortality was not the result of a critical covariate that had been neglected by the Original Investigators." (Krewski et al., 2000, pp. 219-220).

In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and

nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes of the concentration-response relationships warrant additional research in the future.

One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In the Six Cities Study, for which such data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality was reduced (Excess RR = 10.4%, 95% CI = 1.5%, 20%). This would be expected, because the most polluted cities would likely have the greatest decline as pollution controls were applied. Despite this adjustment, the $PM_{2.5}$ effect estimate continued to be positive and statistically significant.

To test the validity of the original ACS air quality data, the Reanalysis Team constructed and applied its own air quality dataset from available historical data. In particular, sulfate levels with and without adjustment were found to differ by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed dataset contained sulfate levels inflated by 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data, while the relative risk of mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis Team found essentially the same results as the original Harvard Six-Cities and ACS studies, even after using independently developed pollution data sets and adjusting for sulfate artifact.

Because of the limited statistical power to conduct most model specification sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study dataset that considered 151 cities. When a range of city-level (ecologic) variables (e.g., population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. The only exception was that associations with fine particles and sulfate were reduced when city-level measures of population change or SO_2 were included in the model.

A major product of the Reanalysis Project is the determination that both pollutant variables and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for addressing this, each of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and were noted to be an important subject for future research.

When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and variation from the spatial correlation between cities, positive associations were still found between mortality and sulfates or fine particles. Results of various models, using alternative methods to address spatial autocorrelation and including different ecologic covariates, found fine particle-mortality associations that ranged from 1.11 to 1.29 (the RR reported by original investigators was 1.17) per 24.5 $\mu g/m^3$ increase in $PM_{2.5}$. With the exception of SO_2, consideration of other pollutants in these models did not alter the associations found with sulfates. The authors reported associations that were stronger for SO_2 than for sulfate, which may indicate that artifactual sulfate was "picking up" some of the SO_2 association, perhaps because the sulfate artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977). It should be recognized that the Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate. The Reanalysis Team concluded: "it suggests that uncontrolled spatial autocorrelation accounts for 24% to 64% of the observed relation. Nonetheless, all our models continued to show an association between elevated risks of mortality and exposure to airborne sulfate" (Krewski et al., 2000, p. 230).

In summary, the reanalyses generally confirmed the original investigators' findings of associations between mortality and long-term exposure to PM, while recognizing that increased mortality may be attributable to more than one ambient air pollution component. Regarding the validity of the published Harvard Six-Cities and ACS Studies, the HEI Reanalysis Report concluded that "Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches

without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

In a further analyses of the Harvard Six City study cohort using a Poisson regression model, Villeneuve et al. (2002) evaluated the relationship between fixed-in-time and time-dependent measures of $PM_{2.5}$ and the risk of mortality among adult, Caucasian participants. The RR of mortality using the Poisson method based upon city-specific exposures that remained constant during the follow up was 1.31 (CI = 1.12 – 1.52), which is similar to results derived from the Cox model used in the original analysis. However, the authors report that "The RR of mortality due to $PM_{2.5}$ exposure decreased when time-dependent measures of air pollution were modeled (Table 8-6). Specifically, when the mean $PM_{2.5}$ level within each city during each period of follow-up was modeled, the RR was 1.16 (95% CI = 1.02 – 1.32). The authors noted that "there were considerable variations in mortality rates across the calendar periods that were modeled," and that "the magnitude of these variations in mortality rates may have dampened any real $PM_{2.5}$ effect on mortality." Villeneuve et al. (2002) concluded that the "attenuated risk of mortality that was observed with a time-dependent index of $PM_{2.5}$ is due to the combined influence of city-specific variations in mortality rates and decreasing levels of air pollution that occurred during follow-up."

Similar results were observed by Villeneuve et al. (2002) irrespective of the exposure window considered. They used various time-dependent indices denoting exposures received in the last two years of follow-up and (b) for exposures lagged 3 – 4 and $\geq$ 5 years. Effect modification was evaluated by fitting interaction terms that consisted of $PM_{2.5}$ exposure and individual risk factors (body mass index, education, smoking, age, gender, and occupational exposure to dusts). The significance of this term was formally tested by constructing a likelihood ratio test statistic. An interaction effect between $PM_{2.5}$ exposure and age was observed ($p < 0.05$), and they therefore presented stratified analysis by age group (< 60, $\geq$ 60 years). For each index of $PM_{2.5}$, the RR of all-cause mortality was more pronounced among subjects < 60 years old. There was no effect modification between $PM_{2.5}$ and the other individual risk factors. The RR for PM-associated mortality did not depend on when exposure occurred in relation to death, possibly because dof little variation between the time-dependent city-specific $PM_{2.5}$ exposure indices ($r > 0.9$) and the fact that the rank ordering of the cities changed little during follow-up.

TABLE 8-6. RELATIVE RISK[a] OF ALL-CAUSE MORTALITY FOR SELECTED INDICES OF EXPOSURE TO FINE PARTICULATE MATTER (per 18.6 μg/m^3) BASED ON MULTIVARIATE POISSON REGRESSION ANALYSIS, BY AGE GROUP, FOR HARVARD SIX CITY STUDY DATA[B]

		Age Group (years)		
Model	**$PM_{2.5}$ Exposure City Specific Index**	**Total**	**< 60**	**≥ 60**
1	Exposure to $PM_{2.5}$ remained fixed over the entire follow up period.	1.31 (1.12 – 1.52)	1.89 (1.32 – 2.69)	1.21 (1.02 – 1.43)
2	Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (no smoothing).[a]	1.19 (1.04 – 1.36)	1.52 (1.15 – 2.00)	1.11 (0.95 – 1.29)
3	Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (smoothed).[b]	1.16 (1.02 – 1.32)	1.43 (1.10 – 1.85)	1.09 (0.93 – 1.26)
4	Time dependent estimate of $PM_{2.5}$ received during the previous two years.	1.16 (1.02 – 1.31)	1.42 (1.09 – 1.82)	1.08 (0.94 – 1.25)
5	Time dependent estimate of $PM_{2.5}$ received 3 - 5 years before current year.	1.14 (1.02 – 1.27)	1.35 (1.08 – 1.87)	1.08 (0.95 – 1.22)
6	Time dependent estimate of $PM_{2.5}$ received > 5 years before current year.	1.14 (1.05 – 1.23)	1.34 (1.11 – 1.59)	1.09 (0.99 – 1.20)

[a] Relative risks were adjusted by age, gender, body mass, index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly.

[b] For each city, exposure to $PM_{2.5}$ was estimated for 13 calendar periods using loglinear regression based on annual mean $PM_{2.5}$ levels. The calendar periods used were: 1970-1978, 1979, 1981, . . . 1989, and 1990+. PM2.5 associations with all-cause mortality assessed for male Caucasian participants in Six Cities Study.

Source: Villeneuve et al. (2002).

8.2.3.2.2 The ACS Study Extension

Pope et al. (2002) extended the analyses (Pope et al., 1995) and reanalyses (Krewski et al., 2000) of the ACS CPS-II cohort to include an additional eight years of follow-up data. The new study has a number of advantages over the previous analyses, in that it (a) doubles the follow-up time from eight to sixteen years and triples the number of deaths; (b) expands the ambient air pollution data substantially, including two recent years of fine particle data and adding data on gaseous co-pollutants; (c) improves statistical adjustments for occupational exposure; (d) incorporates data on dietary covariates believed to be important factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber grains; and (e) uses recent developments in non-parametric spatial smoothing and random effects statistical models as input to the Cox proportional hazards model. Each participant was

identified with a specific metropolitan area, and mean pollutant concentrations were calculated for all metropolitan areas with ambient air monitors in the one to two years prior to enrollment. Ambient pollution during the follow-up period was extracted from the AIRS data base. Averages of daily averages of the gaseous pollutants were used except for ozone, where the average daily 1-hour maximum was calculated for the whole year and for the typical peak ozone quarter (July, August, September). Mean sulfate concentrations for 1990 were calculated from archived quartz filters, virtually eliminating the historical sulfate artifact leading to overestimation of sulfate concentrations.

The Krewski et al. (2000), Burnett et al. (2001a), and Pope et al. (2002) studies were concerned that survival times of participants in nearby locations might not be independent of each other, due to missing, unmeasured, or mis-measured risk factors or their surrogates that may be spatially correlated with air pollution, thus violating an important assumption of the Cox proportional hazards model. Thus, model fitting proceeded in two stages, the first of which was an adjusted relative risk model with a standard Cox proportional hazards model including individual-specific covariates and indicator variables for each metropolitan area, but not air pollutants. In the second stage, the adjusted log(relative risks) were fitted to fine particle concentrations or other air pollutants by a random effects linear regression model.

Models were estimated separately for each of four mortality (total, cardiopulmonary, lung cancer, and causes other than cardiopulmonary or lung cancer deaths) endpoints for the entire follow-up period and for fine particles in three time periods (1979-1983, 1999-2000, and the average of the mean concentrations in these two periods). The results are shown in Table 8-7. Figures 8-9, 8-10, and 8-11 show the results displayed in Figures 2, 3, and 5 of Pope et al. (2002). Figure 8-9 shows that a smooth non-parametric model can be reasonably approximated by a linear model for all-cause mortality, cardiopulmonary mortality, and other mortality; but the log(relative risk) model for lung cancer appears to be non-linear, with a steep linear slope up to an annual mean concentration of about 13 $\mu g/m^3$ and a flatter linear slope at fine particle concentrations > 13 $\mu g/m^3$.

Figure 4 in Pope et al. (2002) shows results for the stratified first-stage models: ages < 60 and > 69 yr are marginally significant for total mortality; ages > 70 are significant for cardiopulmonary mortality; and ages 60-69 for lung cancer mortality. Men are at significantly higher risk for total and lung cancer mortality than are women, but slightly less so for

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 $\mu g/m^3$ $PM_{2.5}$ 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).

cardiopulmonary mortality (although still significant). Log(RR) decreases significantly from individuals with less than to those with more than a high school education, replicating findings in Krewski et al. (2000), but with twice the time on study. Including smoking status showed increased fine particle RR for cardiopulmonary and lung cancer mortality in never-smokers and least effect in current smokers; however, for total mortality, significant or near-significant effects occurred in both current and never-smokers, but not former smokers.

The second-stage random effects models on the right side of Figure 8-10 have much wider confidence intervals than the first-stage models, but are still statistically significant for total, cardiopulmonary, and lung cancer mortality. Spatial smoothing decreased the magnitude and significance of the fine particle effect for total mortality. For cardiopulmonary mortality, spatial smoothing increased the magnitude of the RR and its significance by reducing the width of the confidence intervals in the "50%-span" and "lowest variance" smoothing methods. For lung cancer mortality, spatial smoothing little changed the magnitude of the RR, but increased its significance by reducing the width of confidence intervals in the "50%-span" and "lowest variance" smoothing methods.

Figure 8-11 shows statistically significant relationships between fine particles and total, cardiopulmonary, and lung cancer mortality no matter which averaging span was used for $PM_{2.5}$ and slightly larger effect estimates for the average concentration of the 1979-1983 and 1999-2000 intervals. PM_{15} for 1979-1983 is significantly associated with cardiopulmonary mortality

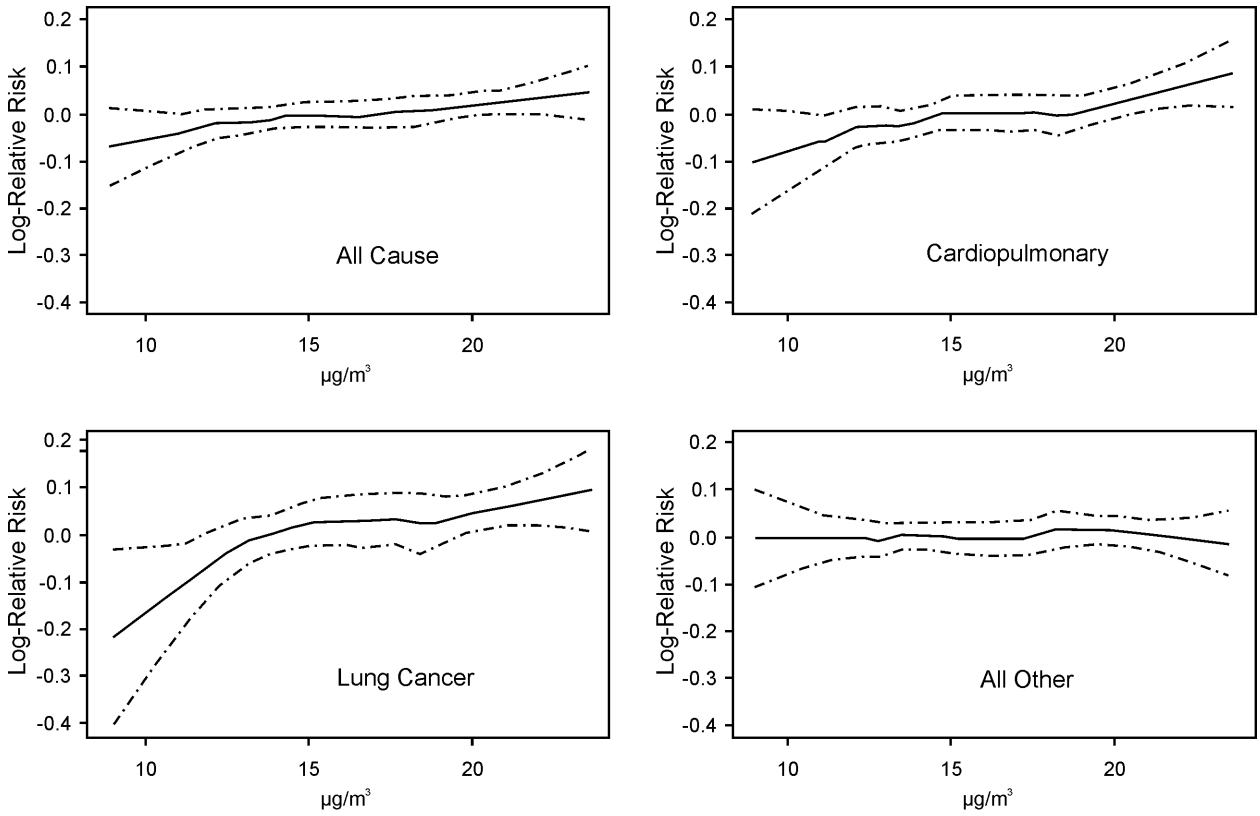

Figure 8-9. Natural logarithm of relative risk for total and cause-specific mortality per 10 µg/m^3 $PM_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions. Based on Pope et al. (2002) mean curve (solid line) with pointwise 95% confidence intervals (dashed lines).

and marginally with total mortality; whereas 1987-1996 PM_{15} is not quite significantly associated with cardiopulmonary mortality. Coarse particles ($PM_{15-2.5}$) and TSP are not significantly associated with any endpoint, but are positively associated with cardiopulmonary mortality. Sulfate particles are very significantly associated with all endpoints, including mortality from all other causes, but only marginally for lung cancer mortality using 1990 filters.

Figure 8-11 also shows highly positive significant relationships between SO_2 and total, cardiopulmonary, and other-causes mortality, but a weaker SO_2 association with lung cancer mortality. Only ozone using only the third quarter for 1982-1998 showed a marginally significant relationship with cardiopulmonary mortality, but not the year-round average. The other criteria pollutants, CO and NO_2, are neither significantly nor positively related to any mortality endpoint, unlike some findings for acute PM exposure-mortality studies.

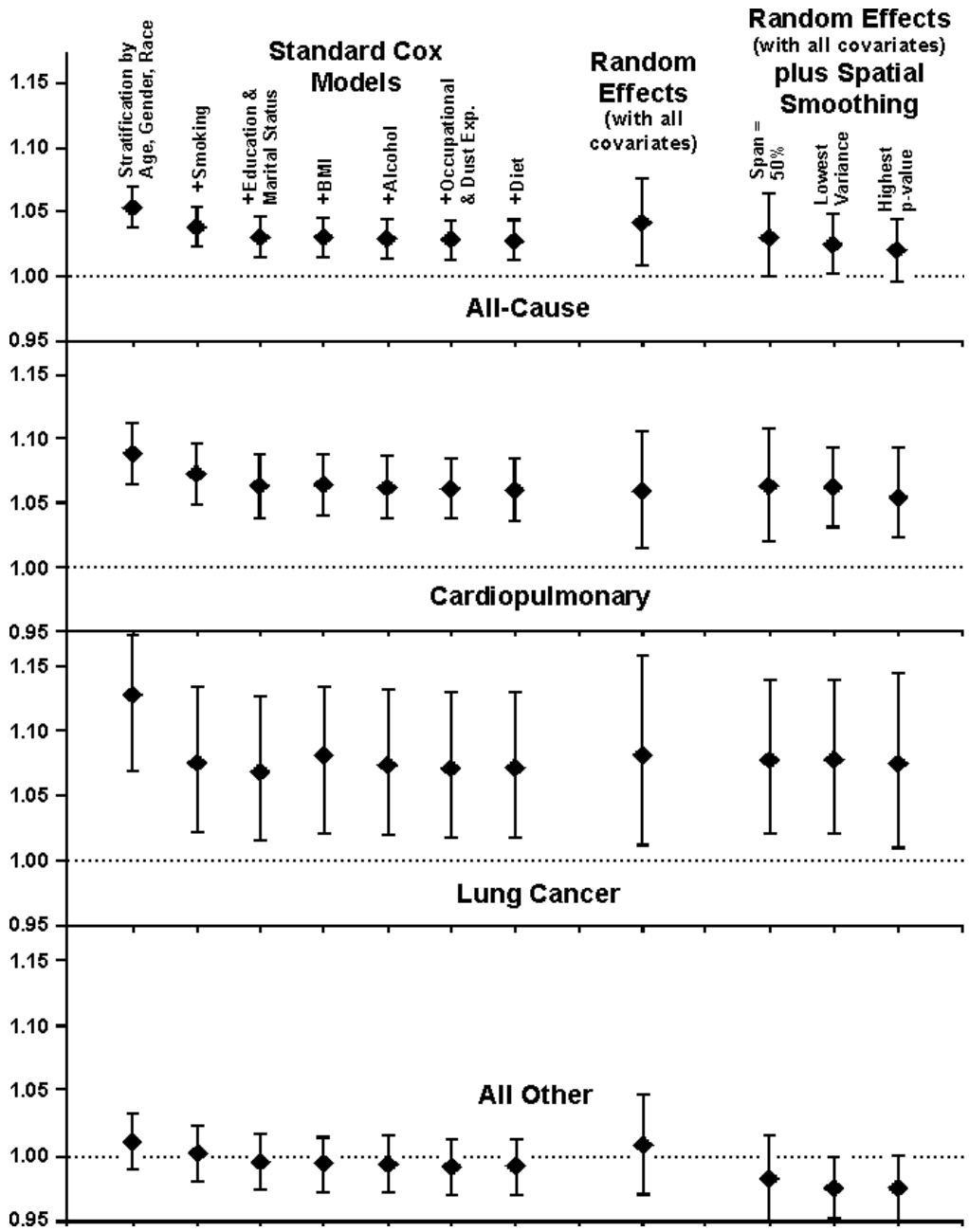

Figure 8-10. Relative risk of total and cause-specific mortality at 10 µg/m^3 $PM_{2.5}$ (mean of 1979-1983) of alternative statistical models. The standard Cox models are built up in a sequential stepwise manner from the baseline model stratified by age, gender, and race by adding additional covariates. 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.

Source: Based on Pope et al. (2002).

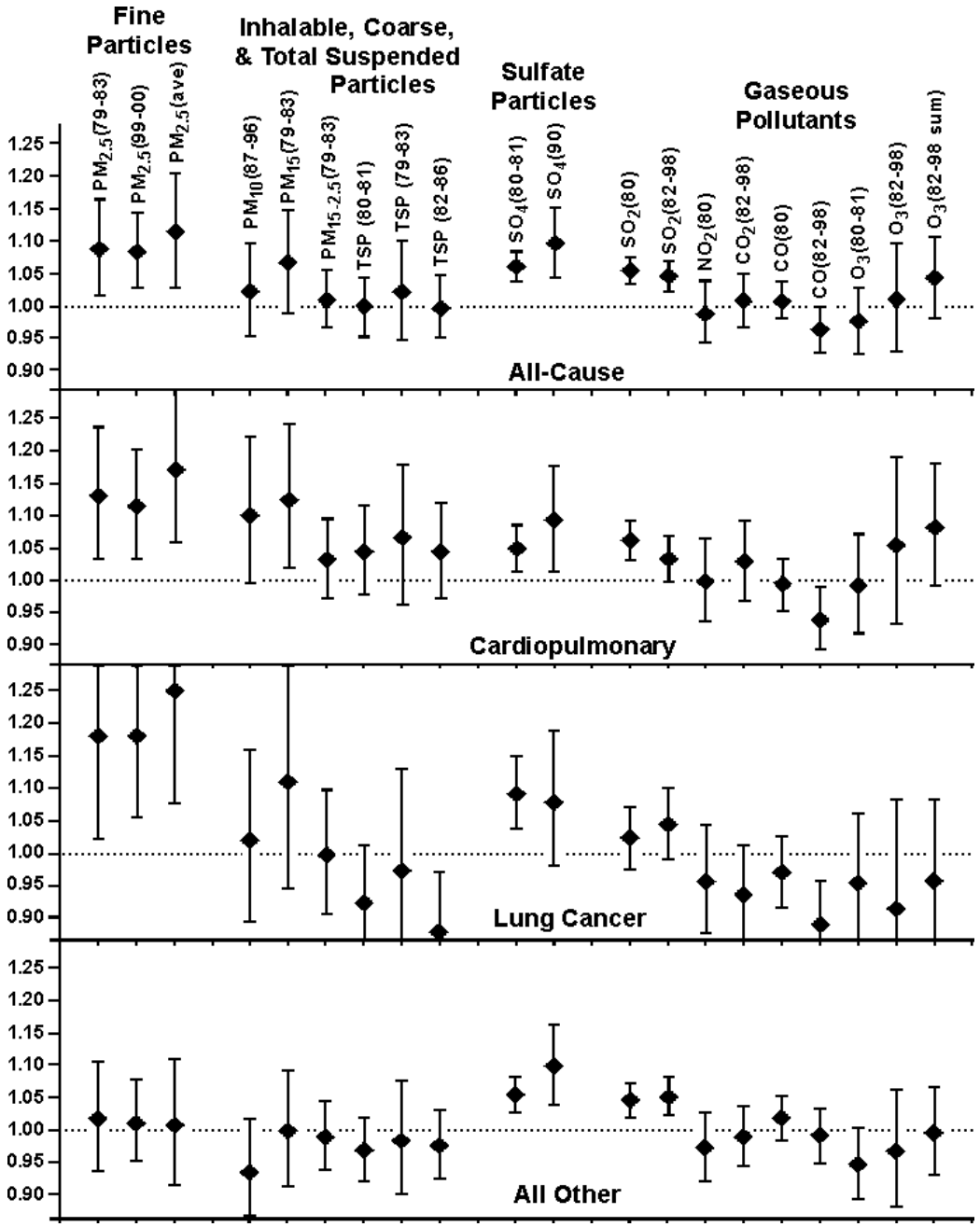

Figure 8-11. Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses).

Source: Based on Pope et al. (2002).

This paper is noteworthy because it confirms that the general pattern of findings in the first eight years of the study (Pope et al., 1995; Krewski et al., 2000) can be reasonably extrapolated to the patterns that remain present with twice the length of time on study and three times the number of deaths. As shown later in Table 8-11, the excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for total mortality in the original ACS study (Pope et al., 1995) was 6.6% (3.6, 9.9%); in the ACS reanalysis (Krewski et al., 2000) it was 7.0% (3.9, 10%); and, in the extended ACS data set (Pope et al., 2002), it was 4.1% (0.8, 7.5%) using the 1979-1983 data and 6.2% (1.6, 11%) using the average of the 1979-1983 and 1999-2000 data. The excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for cardiopulmonary mortality in the original ACS study (Pope et al., 1995) was 12% (6.7, 17%); in the ACS reanalysis (Krewski et al., 2000), it was 12% (7.4, 17%); and, in the extended ACS data set (Pope et al., 2002), it was 5.9% (1.5, 10%) using the 1979-1983 data and 9.3% (3.3, 16%) using the average of the 1979-1983 and 1999-2000 data. Thus, the additional data and statistical analyses reported in Pope et al. (2002) yield somewhat smaller estimates than the original study (Pope et al., 1995), but are similar to estimates from the (Krewski et al. (2000) reanalysis of the original ACS data set.

Based on the above patterns of results, the authors drew the following conclusions:

(1) The apparent association between long-term exposure to fine particle pollution and mortality persists with longer follow-up as the participants in the cohort grow older and more of them die.

(2) The estimated fine particle effect on cardiopulmonary mortality and cancer mortality remained relatively stable even after adjustment for smoking status, although the estimated effect was larger and more significant for never-smokers versus former or current smokers. The estimates were relatively robust against inclusion of many additional covariates: education, marital status, body mass index (BMI), alcohol consumption, occupational exposure, and dietary factors. However, as the authors note, the data on individual risk factors were collected only at the time of enrollment and have not been updated, so that changes in these factors since 1982 could introduce risk-factor exposure mis-classification and a consequent loss of precision in the estimates that might limit the ability to characterize time dependency of effects. Moreover, it is noteworthy that this study found education to be an effect modifier, with larger and more statistically significant PM effect estimates for persons with less education. This may be due to the

fact that less-education is a marker for lower socio-economic status and, therefore, poorer health status and greater pollution susceptibility. These results may also be an indicator that the mobility of the less educated provides better estimates of effects in this study (with no follow up of address changes) than for the more mobile well-educated. In either case, because this cohort comprises a much higher percentage of well-educated persons than the general public, the education effect modification seen suggests that the overall PM effect estimates are likely underestimated by this study cohort versus that which would be found for the general public.

19 (3) Additional assessments for potential spatial or regional differences not controlled in the first-stage model were evaluated. If there are unmeasured or inadequately modeled risk factors that are different across locations or spatially clustered, then PM risk estimates may be biased. If the clustering is independent or random or independent across areas, then adding a random-effects component to the Cox proportional hazards model can address the problem. However, if location is associated with air pollution, then the spatial correlation may be evaluated using non-parametric smoothing methods. No significant spatial auto-correlation was found after controlling for fine particles. Even after adjusting for spatial correlation, the estimated $PM_{2.5}$ effects were significant and persisted for cardiopulmonary mortality and lung cancer mortality and were borderline significant for total mortality, but with much wider confidence intervals after spatial smoothing.

20 (4) Fine particles ($PM_{2.5}$) were associated with elevated total, cardiopulmonary, and lung cancer mortality risks, but not other-cause mortality. PM_{10} for 1987-1996 and PM_{15} for 1979-1983 were just significantly associated with cardiopulmonary mortality, but $PM_{10-2.5}$ and TSP were not associated with total or any cause-specific mortality. All endpoints but lung cancer mortality were very significantly associated with sulfates, except for lung cancer with 1990 sulfate data. All endpoints except lung cancer mortality were significantly associated with SO_2 using 1980 data as were total and other mortality using the 1982-1998 SO_2 data; but cardiopulmonary and lung cancer mortality had only a borderline significant association with the1982-1998 SO_2 data. None of the other gaseous pollutants showed significant positive associations with any endpoint.

Thus, neither coarse thoracic particles nor TSP were significantly associated with mortality; nor were CO and NO_2 on a long-term exposure basis.

(5) The concentration-response curves estimated using non-parametric smoothers were all monotonic and nearly linear (except for lung cancer). However, the shape of the curve may become non-linear at much higher concentrations.

(6) The excess risk from $PM_{2.5}$ exposure is much smaller than that estimated for cigarette smoking for current smokers in the same cohort (Pope et al., 1995): RR = 2.07 for total mortality, RR = 2.28 for cardiopulmonary mortality, and RR = 9.73 for lung cancer mortality. In the more polluted areas of the United States, the relative risk for substantial obesity (a known risk factor for cardiopulmonary mortality) is larger than that for $PM_{2.5}$, but the relative risk from being moderately overweight is somewhat smaller.

8.2.3.2.3 AHSMOG Analyses

The Adventist Health Study of Smog (AHSMOG), a third major U.S. prospective cohort study of chronic PM exposure-mortality effects, started with enrollment in 1977 of 6,338 non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to 95 years. All had resided for at least 10 years within 5 miles (8 km) of their then-current residence locations, either within one of the three major California air basins (San Diego, Los Angeles, or San Francisco) or else were part of a random 10% sample of Adventist Health Study participants residing elsewhere in California. The study has been extensively described and its initial results earlier reported elsewhere (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991).

In more recent AHSMOG analyses (Abbey et al., 1999), the mortality status of subjects after ca. 15-years of follow-up (1977-1992) was determined by various tracing methods and 1,628 deaths (989 female, 639 male) were found in the cohort. This 50% percent increase during the follow-up period (versus previous AHSMOG reports) enhances the power of the latest analyses over past published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029 were cardiopulmonary, 135 were non-malignant respiratory (ICD9 codes 460-529), and 30 were lung cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category, contributing respiratory causes (CRC), which included any mention of nonmalignant respiratory disease as an underlying or "contributing cause" on the death certificate. Numerous

analyses were done for the CRC category, due to the large numbers and relative specificity of respiratory causes as a factor in the deaths. Education was used to index socio-economic status, rather than income. Physical activity and occupational exposure to dust were also used as covariates. Cox proportional hazard models adjusted for a variety of covariates or stratified by sex were used. The "time" variable used in most of the models was survival time from date of enrollment, except that age on study was used for lung cancer effects due to the expected lack of short-term effects. Many covariate adjustments were evaluated, yielding results for all non-external mortality as shown in Table 8-8.

TABLE 8-8. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

Pollution Index	Pollution Increment	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 μg/m^3	0.950	0.873	1.033	1.091	0.985	1.212
SO_4 mean	5 μg/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).

As for cause-specific mortality analyses of the AHSMOG data, positive and statistically significant effects on deaths with underlying contributing respiratory causes were also found for 30 day/yr > 100 μg/m^3 PM_{10} (RR = 1.14, 95% CI = 1.03-1.56) in models that included both sexes and adjustment for age, pack-years of smoking, and BMI. Subsets of the cohort had elevated risks: (a) former smokers had higher RR's than never-smokers (RR for PM_{10} exceedances for never-smokers was marginally significant by itself); (b) subjects with low intake of anti-oxidant vitamins A, C, E had significantly elevated risk of response to PM_{10}, whereas those with adequate intake did not (suggesting that dietary factors or, possibly, other socio-economic or life

style factors for which they are a surrogate may be important covariates); and (c) there also appeared to be a gradient of PM_{10} risk with respect to time spent outdoors, with those who had spent at least 16 h/wk outside being at greater risk from PM_{10} exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal variation in exposure to ambient air pollution is not clear, e.g., if the males spent much more time outdoors than the females, outdoor exposure time could be confounded with gender. When the cardiopulmonary analyses are broken down by gender (Table 8-9), the RR's for female deaths were generally smaller than that for males, but none of the risks for PM indices or gaseous pollutants were statistically significant at $p < 0.05$.

TABLE 8-9. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

Pollution Index	Pollution Increment	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).

The AHSMOG cancer analyses yielded very mixed results for lung cancer mortality (Table 8-10). For example, RR's for lung cancer deaths were statistically significant for males for PM_{10} and O_3 metrics, but not for females. In contrast, such cancer deaths were significant for mean NO_2 only for females (but not for males), but lung cancer metrics for mean SO_2 were significant for both males and females. This pattern is not readily interpretable, but is reasonably attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males), resulting in wide RR confidence intervals and very imprecise effects estimates.

TABLE 8-10. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Increment	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 µg/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 smoker	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).

The analyses reported by Abbey et al. (1999) attempted to separate PM_{10} effects from those of other pollutants by use of two-pollutant models, but no quantitative findings from such models were reported. Abbey et al. did mention that the PM_{10} coefficient for CRC remained stable or increased when other pollutants were added to the model. Lung cancer mortality models for males evaluated co-pollutant effects in detail and indicated that NO_2 was non-significant in all two-pollutant models but the other pollutant coefficients were stable. The PM_{10} and O_3 effects remained stable when SO_2 was added, suggesting possible independent effects, but PM_{10} and O_3 effects were hard to separate because these pollutants were highly correlated in this study. Again, however, the very small number of lung cancer observations and likely great imprecision of reported effects estimates markedly limit the weight that should be accorded to these results.

Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey et al. (1999), but focused on lung cancer incidence (1977-1992). There were only 20 female and 16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be specifically relevant to cancer, these being the annual average of monthly exposure indices from January, 1973 through the following months but ending 3 years before date of diagnosis (i.e., representing a 3-year lag between exposure and diagnosis of lung cancer). The covariates in the Cox proportional hazards model were pack-years of smoking and education, and the time variable was attained age. Many additional covariates were evaluated for inclusion, but only 'current use of alcohol' met criteria for inclusion in the final model. Pollutants evaluated were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant, including outdoor exposure times. The RR estimates for male lung cancer cases were: (a) positive and statistically significant for all PM_{10} indicators; (b) positive and mostly significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in former smokers; (c) positive and significant for mean SO_2, except when restricted to proximate monitors; and (d) positive but not significant for mean NO_2. When analyses are restricted to the use of air quality data within 32 km of the residences of subjects, the RR over the IQR of 24 $\mu g/m^3$ in the full data set is 5.21 (or RR=1.99 per 10 $\mu g/m^3$ PM_{10}). The female RR's were all much smaller than for males, their being significant for mean SO_2 but not for any indicator of PM_{10} or O_3.

The AHSMOG investigators also attempted to compare effects of fine versus coarse particles (McDonnell et al, 2000). For AHSMOG participants living near an airport (n = 3,769), daily $PM_{2.5}$ concentrations were estimated from airport visibility using previously-described methods (Abbey et al, 1995b). Given the smaller numbers of subjects in these subset analyses, it is not necessarily surprising that no pollutants were found to be statistically significant in these regressions, even based on analysis for the male subset near airports (n = 1266). It is important to caveat that (a) the $PM_{2.5}$ exposures were estimated from visibility measurements (increasing exposure measurement error) and yielded a very uneven and clustered distribution of estimated exposures and; (b) the $PM_{10-2.5}$ values were calculated from the differencing of PM_{10} and $PM_{2.5}$, likely contributing to additional measurement error for the coarse particle ($PM_{10-2.5}$) variable used in the analyses.

8.2.3.2.4 The EPRI-Washington University Veterans' Cohort Mortality Study

Lipfert et al. (2000b) reported preliminary results from large-scale mortality analyses for a prospective cohort of up to 70,000 men assembled by the U.S. Veterans Administration (VA) in the mid-1970s. While much smaller than the ACS cohort, this VA study group is similar in that it was not originally formed to study air pollution, but was later linked to air pollution data collected separately, much of it subsequent to the start of the study. The AHSMOG and Six City studies were designed as prospective studies to evaluate long-term effects of air pollution and had concurrent air pollution measurements. The ACS study was also a prospective study, using air pollution data obtained at about the approximate time of enrollment but not subsequently (Pope et al., 1995). The extended ACS data incorporated much more air pollution data, including TSP data back to the 1960s and more recent fine particle data. The VA $PM_{2.5}$ data set was smaller than the TSP data set and similar to the ACS data.

The VA study cohort was male, middle-aged (51 ± 12 years) and included a larger proportion of African-Americans (35%) than the U.S. population as a whole and a large percentage of current or former smokers (81%). The cohort was selected at the time of recruitment as being mildly to moderately hypertensive, with screening diastolic blood pressure (DBP) in the range 90 to 114 mm Hg (mean 96, about 7 mm more than the U.S. population average) and average systolic blood pressure (SBP) of 148 mm Hg. The subjects had all been healthy enough to be in the U.S. armed forces at one time. A comparison of their pre-existing health status at time of study recruitment versus the initial health status of the other cohorts would be of interest. The study that led to the development of this clinical cohort (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970; 1967) was a "landmark" VA cooperative study demonstrating that anti-hypertensive treatment markedly decreased morbidity and mortality (Perry et al., 1982). The clinical cohort itself involved actual clinical rather than research settings. Some differences between the VA cohort and other prospective cohorts are noted below.

Pollutant levels of the county of residence at the time of entry into the study were used for analyses versus levels at the VA hospital area. Contextual socioeconomic variables were also assembled at the ZIP-code and county levels. The ZIP-code level variables were average education, income, and racial mix. County-level variables included altitude, average annual heating-degree days, percentage Hispanic, and socioeconomic indices. Census-tract variables

included poverty rate and racial mix. County-wide air pollution variables included TSP, PM_{10}, $PM_{2.5}$, PM_{15}, $PM_{15\text{-}2.5}$, SO_4, O_3, CO, and NO_2 levels at each of the 32 VA clinics where veterans were enrolled. Besides considering average exposures over the entire period, three sequential mortality follow-up periods (1976-81, 1982-88, 1989-96) were also evaluated in separate statistical analyses that attempted to relate mortality in each of those periods to air pollution in different preceding, concurrent, or subsequent periods (i.e., up to 1975, 1975-81, 1982-88, and 1989-86, for TSP in the first three periods, PM_{10} for the last, and NO_2, 95th percentile O_3, and 95^{th} percentile CO for all four periods). Mortality in the above-noted periods was also evaluated in relation to SO_4 in each of the same four periods noted for NO_2, O_3, and CO, and to $PM_{2.5}$, PM_{15}, and $PM_{15\text{-}2.5}$ in 1979-81 and 1982-84.

The participants in the VA Cohort clearly formed an "at-risk" population, and the results by Vasan et al. (2001) make more plausible the hypothesis stated in Lipfert et al. (2000b, p. 62) that ". . . the relatively high fraction of mortality within this cohort may have depleted it of susceptible individuals in the later periods of follow-up." The use of diastolic and systolic blood pressure in the reported regression results may require further evaluation. The role of DBP and SBP as predictors in regression models in the VA Cohort may be considered as closer to the endpoint (mortality) than as a more distal behavioral, environmental, or contextual predictor of mortality such as air pollution, temperature, smoking behavior, BMI, etc. Personal-level variables tend to interact only with each other, as do county-level variables, with little correlation across spatial scales.

The estimated mean risk of cigarette smoking in this cohort (RR = 1.43) is also smaller than that of the Six City cohort (RR = 1.59) and the ACS cohort (RR = 2.07 for current smokers). Some possible differences include the higher proportion of former or current smokers in this cohort (81%) versus 51% in the ACS study and 42 to 53% in the Six City study. A possibly more important factor may be the difference in education levels, as only 12% of the ACS participants had less than a high school education vs 28% of the Six City cohort. Education level was not reported for the VA Cohort. Education differences may be associated with smoking behavior, and the large number of interaction terms used in the VA study model may also partially to account for differences in results obtained across the three ACS, Six-City, VA) studies.

The preliminary screening models used proportional hazards regression models (Miller et al., 1994) to identify age, SBP, DBP, BMI (nonlinear), age and race interaction terms, and present or former smoking as baseline predictors, with one or two pollution variables added. In the final model using 233 terms (of which 162 were interactions of categorized SBP, DBP, and BMI variables with age), the most significant non-pollution variables were SBP, DBP, BMI, and their interactions with age, smoking status, average education, race, poverty, height, and a clinic-specific effect. Lipfert et al. (2000b) noted that the risk of current cigarette smoking (1.43) that they found was lower than reported in other studies. The most consistently positive effects were found for O_3 and NO_2 exposures in the immediately preceding years. This study used peak O_3 rather than mean O_3 as in some other cohort studies. This may account for the higher O_3 and NO_2 effects here. While the PM analyses considering segmented (shorter) time periods gave differing results (including significantly negative mortality coefficients for some PM metrics), when methods consistent with the past studies were used (i.e., many- year average PM concentrations), similar results were reported: the authors found that "(t)he single-mortality-period responses without ecological variables are qualitatively similar to what has been reported before ($SO_4 \geq PM_{2.5} > PM_{15}$)." With ecological variables included, the only significant PM effect was that of TSP up to 1981 on 1976-81 mortality. It might be instructive to evaluate more parsimonious regression models with fewer ecological covariates and interaction terms. It is noteworthy that estimated PM effects appear to be smaller in the later years of the study rather than in the earlier years. This may also be due to cohort depletion.

Overall, the authors concluded that "the implied mortality risks of long-term exposure to air pollution were found to be sensitive to the details of the regression model, the time period of exposure, the locations included, and the inclusion of ecological as well as personal variables."

8.2.3.2.5 Relationship of AHSMOG, Six Cities, ACS and VA Study Findings

The results of the more recent AHSMOG mortality analyses (Abbey et al., 1999; McDonnell et al., 2000) are compared here with findings from the earlier Six Cities study (Dockery et al., 1993), the ACS study (Pope et al., 1995), the HEI reanalyses of the latter two studies, the extension of the ACS study (Pope et al., 2002), and the VA study (Lipfert et al., 2000b). Table 8-11 compares the estimated RR for total, cardiopulmonary, and cancer mortality among the studies. The number of subjects in these studies varies greatly: 8,111 subjects in the

TABLE 8-11. COMPARISON OF EXCESS RELATIVE RISKS OF LONG-TERM MORTALITY IN THE HARVARD SIX CITIES, ACS, AHSMOG, AND VA STUDIES

		Total Mortality		Cardiopulmonary Mortality		Lung Cancer Mortality	
Study	PM[1]	Ex. RR[2]	95% CI	Ex. RR	95% CI	Ex. RR	95% CI
Six City[3]	$PM_{2.5}$	13%	(4.2, 23%)	18%	(6.0, 32%)	18%	(−11, 57%)
Six City New[4]	$PM_{2.5}$	14%	(5.4, 23%)	19%	(6.5, 33%)	21%	(−8.4, 60%)
ACS[5]	$PM_{2.5}$	6.6%	(3.5, 9.8%)	12%	(6.7, 17%)	1.2%	(−8,7, 12%)
ACS[6] New	$PM_{2.5}$	7.0%	(3.9, 10%)	12%	(7.4, 17%)	0.8%	(−8.7, 11%)
ACS New	$PM_{15-2.5}$	0.4%	(−1.4, 2.2%)	0.4%	(−2.2%, 3.1%)	−1.2%	(−7.3%, 5.1%)
ACS New	$PM_{10/15}$ Dichot	4.1%	(0.9, 7.4%)	7.3%	(3.0, 12%)	0.8%	(−8.1, 11%)
ACS New	$PM_{10/15}$ SSI	1.6%	(−0.8, 4.1%)	5.7%	(2.5, 9.0%)	−1.6%	(−9.1, 6.4%)
ACS Extend.[7]	$PM_{2.5}$ 1979-83	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]	$PM_{10/15}$	2.1%	(−4.5, 9.2%)	0.6%	(−7.8, 10%)	81%	(14, 186%)
AHSMOG[9]	$PM_{2.5}$	8.5%	(−2.3, 21%)	23%	(−3.0, 55%)	39%	(−21, 150%)
AHSMOG[10]	PM_{10-25}	5.2%	(−8.3, 21%)	20%	(−13, 64%)	26%	(−38, 155%)
VA[10]	$PM_{2.5}$	−10.0%	(−15, −4.6%)				

[1]Increments are 10 μg/m^3 for $PM_{2.5}$ and 20 μg/m^3 for $PM_{10/15}$.
[2]Ex.RR (excess relative risk, percent) = 100 * (RR - 1) where the RR has been converted from the highest-to-lowest range to the standard increment (10 or 20) by the equation.
RR = exp(log(RR for range) × /range).
[3]From (Dockery et al., 1993; Krewski et al., 2000, Part II, Table 21a), original model.
[4]From (Krewski et al., 2000), Part I, Table 21c.
[5]From (Krewski et al., 2000), Part I, Table 25a.
[6]From (Krewski et al., 2000), Part I, Table 25c.
[7]From (Pope et al., 2002).
[8]From (Abbey et al., 1999), pooled estimate for males and females.
[9]From (McDonnell et al., 2000), using two-pollutant (fine and coarse particle) models; males only.
[10]Males only, exposure period 1979-81, mortality 1982-88 from Table 7 (Lipfert et al., 2000b).

Six-Cities Study; 295,223 subjects in the 50 fine particle ($PM_{2.5}$) cities and 552,138 subjects in the 151 sulfate cities of the ACS Study; 6,338 in the AHSMOG Study; and 70,000 in the VA study. This may partially account for differences among their results.

The Six Cities study found significant associations of $PM_{2.5}$ with total and cardiopulmonary (but not lung cancer) mortality, but not with coarse particle indicators. In the Krewski et al. (2000) reanalysis of the ACS study data, significant associations were found for both $PM_{2.5}$ and PM_{15} (excess relative risks of 6.6% for 10 $\mu g/m^3$ $PM_{2.5}$ and 4% for 20 $\mu g/m^3$ increments in annual $PM_{10/15}$, respectively). The results most recently reported for the AHSMOG study (Abbey et al., 1999; McDonnell et al., 2000) used PM_{10} as its PM mass index and found some significant associations with total mortality and deaths with contributing respiratory causes, even after controlling for potentially confounding factors (including other pollutants). However no pattern of consistent, statistically significant associations between mortality and long-term PM exposure was found. The VA study (Lipfert et al., 2000b), also did not find any association with $PM_{2.5}$. The lack of consistent findings in the AHSMOG study and negative results of the VA study, do not negate the findings of the Six Cities and ACS studies: the ACS studies had a substantially larger study population, and both the Six Cities and ACS studies were based on measured PM data (in contrast with AHSMOG PM estimates based on TSP or visibility measurements) and have been validated through exhaustive reanalyses. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient PM (especially fine PM) exposure and mortality.

There is no clear consistency in relationships among PM effect sizes, gender, and smoking status across these studies. The AHSMOG study cohort is a primarily nonsmoker group while the VA study cohort had a large proportion of smokers and former smokers in an all-male population. The ACS results, show similar and significant associations with total mortality for both “never smokers” and “ever smokers”, although the ACS cohort may include a substantial number of long-term former smokers with much lower risk than current smokers. The Six Cities study cohort shows the strongest evidence of a higher PM effect in current smokers than in non-smokers, with female former smokers having a higher risk than male former smokers. This study suggests that smoking status may be viewed as an effect modifier for ambient PM, just as smoking may be a health effect modifier for ambient O_3 (Cassino et al., 1999).

When the ACS study results are compared with the AHSMOG study results for SO_4^{-2} ($PM_{10-2.5}$ and PM_{10} were not considered in the ACS study, but were evaluated in ACS reanalyses [Krewski et al., 2000; Pope et al, 2002]), the total mortality effect sizes per 15 $\mu g/m^3$ SO_4^{-2} for the males in the AHSMOG population fell between the Six-Cities and the ACS effect-size estimates for males (RR = 1.28 for AHSMOG male participants; RR=1.61 for Six-Cities Study male non-smokers; and RR = 1.10 for never smoker males in the ACS study), and the AHSMOG study 95% confidence intervals encompass both of those other studies' sulfate RR's.

8.2.3.2.6 The S-Plus GAM Convergence Problem and Cohort Studies

The long-term pollution-mortality effect study results discussed above in this section were unaffected by the GAM default convergence issue reported by Dominici et al. (2002) and discussed earlier in this chapter, because they did not use such a model specification. Instead, the cohort studies of long-term PM exposures used Cox Proportional Hazards models. For example, in the recent Pope et al. study (2002), the baseline models were random effects Cox Proportional Hazards models without the inclusion of nonparametric smooths. However, Pope et al. (2002) did include a non-parametric spatial smooth in the model as part of a more extended sensitivity analysis to evaluate more aggressive control of spatial differences in mortality. They found that the estimated pollution-mortality effects were not sensitive to this additional spatial control, so the final reported results did not include the smooth; and this study's results, like those from the other cohort studies discussed above, were not affected by the S-Plus convergence issue.

8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition

8.2.3.3.1 Six Cities, ACS, and AHSMOG Study Results

Ambient PM consists of mixtures that may vary in composition over time and from place to place. This should logically affect the relative toxicity of PM indexed by mass at different times or locations. Some semi-individual chronic exposure studies have investigated relative roles of various PM components in contributing to observed air pollution associations with mortality. However, only a limited number of the chronic exposure studies have included direct measurements of chemical-specific constituents of the PM mixes indexed by mass measurements used in their analyses.

As shown in Table 8-12, the Harvard Six-Cities Study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and SO_4^{-2} RR associations (as indicated by their respective 95% CI's and t-statistics) were more consistent than those for the coarser mass components. Further, the effects of sulfate and non-sulfate $PM_{2.5}$ are quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities; consequently, the Six-Cities results were much less conclusive for the acidic component of PM than for the other PM metrics measured over many years during the study.

TABLE 8-12. 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 8-13 presents comparative $PM_{2.5}$ and SO_4^{-2} results from the ACS study, indicating that both had substantial, statistically significant effects on all-cause and cardiopulmonary mortality. On the other hand, the RR for lung cancer was notably larger (and substantially more significant) for SO_4^{-2} than $PM_{2.5}$ (not significant). The most recent AHSMOG analyses also considered SO_4^{-2} as a PM index for all health outcomes studied except lung cancer, but SO_4^{-2} was not as strongly associated as PM_{10} with mortality and was not statistically significant for any mortality category.

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^{-2}. There were no significant positive effects for any

TABLE 8-13. 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 µg/m^3)			$PM_{2.5}$ (Range = 24.5 µg/m^3)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

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 8-14 (for total mortality) and Table 8-15 (for cause-specific mortality). Results for the VA study are not shown in Tables 8-14 and 8-15 for two reasons. First, the VA cohort is all male and largely consists of current or former smokers (81%) and is thusly not comparable to the total or male non-smoker populations of the other studies. Secondly, the VA study analyzed a wide variety of exposure periods and mortality periods, making it difficult to summarize or compare the VA results.

Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the most versus least polluted city in Table 3 of Dockery et al. (1993), adjusted to standard increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection Agency (1996a). The Six Cities study of eastern and mid-western U.S. cities suggests a strong and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly significant relationship to PM_{10}, and a marginal relationship to $PM_{10-2.5}$. The ACS study looked at a broader spatial representation of cities, and found a stronger statistically significant relationship to $PM_{2.5}$ than to sulfate (no other pollutants were examined). The AHSMOG study at California sites (where sulfate levels are typically low) found significant effects in males for PM_{10} 100 µg/m^3 exceedances and a marginal effect of mean PM_{10}, but no PM effects for females or with sulfates. On balance, the overall results shown in Tables 8-14 and 8-15 suggest

TABLE 8-14. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 μg/m^3)	Six Cities	All	1.50[a]; 1.53[b]	2.94[a]; 3.27[b]
		Male Nonsmoker	1.28[a]	0.81[a]
	AHSMOG	Male Nonsmoker	1.24	1.61
$PM_{2.5}$ (25 μg/m^3)	Six Cities	All	1.36[a]; 1.38[b]	2.94[a]; 3.73[b]
		Male Nonsmoker	1.21[a]	0.81[a]
	ACS (50 cities)	All	1.17	4.35
		Male Nonsmoker	1.25	1.96
SO_4 = (15 μg/m^3)	Six Cities	All	1.50[a]; 1.57[b]	2.94[a]; 3.67[b]
		Male Nonsmoker	1.35	0.81[a]
	ACS (151 cities)	All	1.11	5.11
		Male Nonsmoker	1.10	1.59
	AHSMOG	Male Nonsmoker	1.28	0.96
Days/yr. with PM_{10} > 100 μg/m^3 (30 days)	AHSMOG	Male Nonsmoker	1.08	2.18
$PM_{10-2.5}$ (25 μg/m^3)	Six Cities	All	1.81[a]; 1.56[b]	2.94[a,c] 1.81[b]
		Male Nonsmoker	1.43[a]	0.81[a]

[a]Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b]Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996a).
[c]Method 1 not recommended for $PM_{10-2.5}$ analysis, due to high concentration in Topeka.

statistically significant relationships between long-term exposures to PM_{10}, $PM_{2.5}$, and/or sulfates and excess total and cause-specific cardiopulmonary mortality.

The semi-individual long-term PM exposure studies conducted to date collectively appear to confirm earlier cross-sectional study indications that the fine mass component of PM_{10} (and usually especially its sulfate constituent) are more strongly correlated with mortality than is the coarse $PM_{10-2.5}$ component. However, the greater precision of $PM_{2.5}$ population exposure measurement (both analytical and spatial) relative to $PM_{10-2.5}$ makes conclusions regarding their

TABLE 8-15. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 µg/m^3)	Six Cities	All	1.744[a]	2.94[a]
	AHSMOG	Male Nonsmoker	1.219	1.120
		Male Non-CRC[c]	1.537	2.369
$PM_{2.5}$ (25 µg/m^3)	Six Cities	All	1.527[a]	2.94[a]
	ACS (50 cities)	All	1.317	4.699
		Male	1.245	3.061
		Male Nonsmoker	1.245	1.466
SO_4= (15 µg/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 µg/m^3)	Six Cities	All	2.251[a]	2.94[a,b]

[a]Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b]Method 1 not recommended for $PM_{10-2.5}$ analysis due to high concentration in Topeka.
[c]Male non. - CRC = AHSMOG subjects who died of any contributing non-malignant respiratory cause.

relative contributions to observed PM_{10}-related associations less certain than if the effect of their relative errors of measurement could be addressed.

8.2.3.3.2 Lipfert and Morris (2002): An Ecological Study

Although reasons were identified for preferring to use prospective cohort studies to assess the long-term exposure effects of particles and gases, additional useful information may still be derived from ecological studies, particularly by repeated cross-sectional studies that may provide another tool for examining changes in air-pollution-attributable mortality over time. Lipfert and

Morris (2002) carried out cross-sectional regressions for five time periods using published data on mortality, air pollution, climate, and socio-demographic factors using county- level data. Data were available for TSP and gaseous co-pollutants as far back as 1960 and for $PM_{2.5}$, PM_{15}, and $SO_4^{=}$ from the inhalable particular network (IPN). Attributable mortality at ages 45+ for 1979-1981 was reported to be associated with 1960-64 TSP, less strongly with 1970-1974 TSP, but not with concurrent (1979-1981) TSP. Attributable mortality for ages 45+in 1979-1981 was associated with $PM_{2.5}$ and SO_4^{-2} but not with PM_{15} for 1979-1984. However, SO_4^{-2} for most intervals from 1960-64 up to 1979-1981 was associated with mortality for most ages. Concurrent SO_2 (1979-1981) was associated with mortality, but much less for earlier years.

Pollution-attributable mortality in 1989-91 was no longer significantly associated with TSP, but remained significantly associated with $PM_{2.5}$ and SO_4^{-2} for ages 45+ for most time intervals: 1979-84 and 1999 for $PM_{2.5}$; 1970-74, 1979-81, 1979-84 for fine); and 1982-88 for SO_4^{-2}. Pollution-attributable mortality in 1995-1997 had little association with present or previous $PM_{2.5}$ and PM_{10}, but a reasonably consistent and positive relationship to SO_4^{-2}. There appeared to be a systematic decrease in the TSP, IPN, $PM_{2.5}$, and PM_{10} effects from the 1960s to the 1990s and in the AIRS and IPN SO_4^{-2} effect over time, but an increase in the AIRS $PM_{2.5}$ effect and in the NO_2 and peak O_3 effects.

One of the journal editors (Ayres, 2002) notes that this study uses some other ecological variables that may improve the model. Two of the ecological variables, vehicle miles of travel per square mile per year by gasoline (VMTG) and diesel (VMTD) vehicles, respectively, in a county (also used in Janssen et al., 2002) are likely to have important associations with air pollution. As noted earlier, some ambient pollutants associated with fuel combustion have higher concentrations near main roads, such as $PM_{10-2.5}$ (EC if from diesel exhaust) , NO_2, and CO; whereas other pollutants (such as O_3) may have higher concentrations away from major highways. Similarly, some models employed included the percentage of air conditioning in a county, a factor that may well be correlated with greater secondary aerosol formation in warmer temperatures and is likely associated with diminished exposure to air pollution, resulting in smaller acute health effects per $\mu g/m^3$ of PM pollution (Janssen et al, 2002). Given these potentially confounding terms in this study's model, it is not surprising that the authors find somewhat lower percentage increases in mortality per $\mu g/m^3$ of PM than in the above-discussed cohort studies.

8.2.3.4 Population-Based Mortality Studies in Children

Some older cross-sectional mortality studies reviewed in the 1996 PM AQCD suggested that the young may represent a susceptible sub-population for PM-related mortality. For example, Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages < 1 mo) and post-neonatal mortality (ages 1-12 mo) in the Czech Republic and reported significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. The exposure duration was longer than a few days, but shorter than in the adult prospective cohort studies. Thus, the limited available studies reviewed in the 1996 PM AQCD were highly suggestive of an association between ambient PM concentrations and infant mortality, especially among post-neonatal infants.

More recent studies since the 1996 PM AQCD have focused specifically on ambient PM relationships to (a) intrauterine mortality and morbidity and (b) early post neonatal mortality. In a study by Pereira et al. (1998) of intrauterine (pre-natal) mortality during one year (1991-1992) in Brazil, PM_{10} was not found to be a significant predictor, but involvement of CO was suggested by an association between increased carboxyhemoglobin (CoHb) in fetal blood and ambient CO levels on the day of delivery measured in a separate study. Another study (Dejmek et al., 1999) evaluated possible impacts of ambient PM_{10} and $PM_{2.5}$ exposure (monitored by EPA-developed VAPS methods) during pregnancy on intrauterine growth retardation (IUGR) risk in the highly polluted Teplice District of Northern Bohemia in the Czech Republic during three years (1993-1996). Mean levels of pollutants (PM, NO_2, SO_2) were calculated for each month of gestation and three concentration intervals (low, medium, high) were derived for each pollutant. Preliminary analyses found significant associations of IUGR with SO_2 and PM_{10} early in pregnancy but not with NO_2. Odds ratios for IUGR for PM_{10} and $PM_{2.5}$ levels were determined by logistic regressions for each month during gestation, after adjusting for potential confounding factors (e.g., smoking, alcohol consumption during pregnancy, etc.). Definition of an IUGR birth was any one for which the birth weight fell below the 10^{th} percentile by gender and age for live births in the Czech Republic (1992-93). The ORs for IUGR were significantly related to PM_{10} during the first month of gestation: that is, as

compared to low PM_{10}, the medium level PM_{10} OR = 1.47 (CI 0.99-2.16), and the high level PM_{10} OR = 1.85 (CI 1.29-2.66). $PM_{2.5}$ levels were highly correlated with PM_{10} (r = 0.98) and manifested similar patterns (OR = 1.16, CI 0.08-0.69 for medium $PM_{2.5}$ level; OR = 1.68, CI 1.18-2.40 for high $PM_{2.5}$ level). These results suggest effects of PM exposures (probably including fine particles such as sulfates, acid aerosols, and PAHs in the Teplice ambient mix) early in pregnancy (circa embryo implantation) on fetal growth and development.

More consistent results indicating likely early post-natal PM exposure effects on neonatal infant mortality have emerged from other new studies. Woodruff et al. (1997), for example, used cross-sectional methods to evaluate possible association of post-neonatal mortality with ambient PM_{10} pollution. This study involved an analysis of a cohort of circa 4 million infants born during 1989-1991 in 86 U.S. metropolitan statistical areas (MSAs). Data from the National Center for Health Statistics-linked birth/infant death records were combined at the MSA level with PM_{10} data from EPA's Aerometric database. Infants were categorized as having high, medium, or low exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Relationships between this early neonatal PM_{10} exposure and total and cause-specific post-neonatal mortality rates (from 1 mo to 1 y of age) were examined using logistic regression analyses, adjusting for demographic and environmental factors. Overall post-neonatal mortality rates per 1,000 live births were 3.1 among infants in areas with low PM_{10} exposures, 3.5 among infants with medium PM_{10} exposures, and 3.7 among highly PM exposed infants. After adjustment for covariates, the OR and 95% confidence intervals for total post-neonatal mortality for the high versus the low exposure group was 1.10 (CI = 1.04-1.16). For normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI = 1.05-1.85) and sudden infant death syndrome (OR = 1.26, CI = 1.14-1.39). Among low birth weight babies, high PM_{10} exposure was positively (but not significantly) associated with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61). However, other pollutants (e.g., CO) were not considered as possible confounders. This study provides results consistent with some earlier reports indicating that outdoor PM air pollution may be associated with increased risk of post-neonatal mortality (e.g., Bobak and Leon, 1992), but lack of consideration of other air pollutants as potential confounders in this new study reduces the certainty that PM is the specific causal outdoor air pollutant in this case.

Lipfert et al. (2000c) have reported replicating the basic findings of Woodruff et al. (1997) using a similar modeling approach but annual average PM_{10} air quality data for one year (1990) instead of PM_{10} averaged over the first two post natal months during 1989-1991. The quantitative relationship between the individual risk of infant mortality did not differ among infant categories (by age, by birthweight, or by cause), but PM_{10} risks for SIDs deaths were higher for babies of smoking mothers. SO_4^{-2} was a strong negative predictor of SIDs mortality for all age and birth weight categories. The authors (a) noted difficulties in ascribing the reported PM_{10} and SO_4^{-2} associations to effects of the PM pollutants per se versus the results possibly reflecting interrelationships between the air pollution indices, a strong well-established East-West gradient in U.S. SIDS cases, and/or underlying sociodemographic factors (e.g., the socioeconomic or education level of parents) and (b) hypothesized that a parallel gradient in use of wood burning in fireplaces or woodstoves and consequent indoor wood smoke exposure might explain the observed cross-sectional study results.

The basic findings from Woodruff et al. (1997) also appear to be bolstered by a more recent follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles and nitrogen oxides on risk of death in the neonatal and early post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and specific for respiratory causes. Only PM showed a consistent association when all pollutants were entered in one model. Thus, in this study, it appears that long-term exposure to PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

Chay and Greenstone (2001a,b) also conducted a study of changes in annual air pollution and infant mortality over time (rather than spatially) in the U.S. for the period 1981-1982. These studies used sharp, differential air quality changes across sites attributable to geographic variation in the effects of the 1981-1982 recession to estimate the relationship between PM air pollution and infant mortality. During the narrow period of these two years, there was substantial variation across counties in changes in particulate (TSP) pollution and these differential pollution reductions appeared to be independent of changes in numerous socioeconomic and health care factors that may be related to infant mortality. The authors found

that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per 100,000 live births at the county level (a 0.35-0.45 elasticity), the estimates being remarkably stable across a variety of specifications. The estimated effects in this study were driven almost entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal), suggesting that fetal exposure to pollution (via the mother) may have adverse health consequences. Findings of the population reductions in infant birth weight in this study provide evidence consistent with the infant mortality effects found, suggestive of a causal relationship between PM exposure and infant mortality.

The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995 adds additional interesting information pointing towards likely fine particle effects on infant mortality. That is, in Mexico City (where mean 24-h $PM_{2.5}$ = 27.4 μg/m^3), infant mortality was found to be associated with $PM_{2.5}$, NO_2, and O_3 in single pollutant GAM Poisson models, but much less consistently with NO_2 and O_3 than $PM_{2.5}$ in multipollutant models. The estimated excess risk for $PM_{2.5}$-related infant mortality lagged 3-5 days was 18.2% (CI = 6.4-30.7) per 25 μg/m^3 $PM_{2.5}$. The extent to which such a notable increased risk for infant mortality might be extrapolated to U.S. situations is not clear, however, due to possible differences in prenatal maternal or early postnatal infant nutritional status.

8.2.3.5 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects

A review of the studies summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996a) indicates that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins. The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflected cumulative PM effects above and beyond those exerted by acute exposure events.

The recent HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) "replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality." Several questions, including the questions (1-4) posed at the outset of this Section (8.2.3) were investigated by the Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies

data sets. Key results emerging from the HEI reanalyses and other new chronic PM mortality studies are as follow:

(1) A much larger number of confounding variables and effects modifiers were considered in the Reanalysis Study than in the original Six City and ACS studies. The only significant air pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2, which greatly decreased the $PM_{2.5}$ and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38). A similar reduction in particle effects occurred in any multi-pollutant model with SO_2. The most important new effects modifier was education. The AHSMOG study suggested that other metrics for air pollution, and other personal covariates such as time spent outdoors and consumption of anti-oxidant vitamins, might be useful. Both individual-level covariates and ecological-level covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated.

(2) Specific attribution of excess long-term mortality to any specific particle component or gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$ and sulfate were significantly associated with excess total mortality and cardiopulmonary mortality and to about the same extent whether the air pollution data were mean or median long-term concentrations or whether based on original investigator or Reanalysis Team data. The association of mortality with PM_{15} was much smaller, though still significant; and the associations with the coarse fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was significant only for sulfate with the original investigator data or for new investigators with regional sulfate artifact adjustment for the 1980-1981 data (Krewski et al., 2000, Part II, Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous co-pollutants were generally non-significant except for SO_2 (Krewski et al., 2000, Part II, Tables 32, 34-38), which was highly significant, and for cardiopulmonary disease with warm-season ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very high; and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000, p. 234) concluded that, "Collectively, our reanalyses suggest that mortality may be associated with more than one component of the complex mix of ambient air pollutants in urban areas of the United States." In the most recent extension of the ACS study, Pope et al. (2002) confirmed the strong association with SO_2 but found little evidence of effects for long-term exposures to other gaseous pollutants.

(3) The extensive temporal data on air pollution concentrations over time in the Six City Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure to a much greater extent than reported in Dockery et al. (1993). The first approach was to estimate the log-hazard ratio as a function of follow up time using a flexible spline-function model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4^{-2} and $PM_{2.5}$ suggest very similar relationships, with larger risk after initial exposure decreasing to 0 after about 4 or 5 years, and a large increase in risk at about 10 years follow-up time.

The analyses of the ACS Study proceeded somewhat differently, with less temporal data but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of estimated cumulative exposure (not defined) were very nonlinear and showed quite different relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the mortality log-hazard ratio increasing up to about 15 $\mu g/m^3$ and relatively flat above about 22 $\mu g/m^3$, then increasing again. The sulfate relationship is almost piecewise linear, with a low near- zero slope below about 11 $\mu g/m^3$ and a steep increase above that concentration.

A third approach evaluated several time-dependent $PM_{2.5}$ exposure indicators in the Six City Study: (a) constant (at the mean) over the entire follow-up period; (b) annual mean within each of the 13 years of the study; (c) city-specific mean concentration for the earliest years of the study (i.e., very long-term effect); (d) exposure estimate in 2 years preceding death; (e) exposure estimate in 3 to 5 years preceding death; and (f) exposure estimate > 5 years preceding death. The time-dependent estimates (a-e) for mortality risk are generally similar and statistically significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per 24.5 $\mu g/m^3$ being much lower than the risk of 1.31 estimated for exposure at the constant mean for the period. Thus, it is highly likely the duration and time patterns of long-term exposure affect the risk of mortality; and further study of this question (along with that of mortality displacement from short-term exposures) would improve estimates of life-years lost from PM exposure.

(4) The Reanalysis Study also advanced our understanding of the shape of the relationship between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II, Figure 6) found a visually near-linear relationship between all-cause and cardiopulmonary mortality residuals and mean sulfate concentrations, near-linear between cardiopulmonary mortality and mean $PM_{2.5}$, but a somewhat nonlinear relationship between all-cause mortality

residuals and mean $PM_{2.5}$ concentrations that flattens above about 20 $\mu g/m^3$. The confidence bands around the fitted curves are very wide, however, neither requiring a linear relationship nor precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality relationship for other indicators may be useful in identifying a threshold, if one exists, for chronic PM exposures.

(5) With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies have generally found the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality. While relative measurement errors of various PM indicators must be further evaluated as a possible source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective 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 effects of ambient PM on morbidity endpoints are assessed below in several subsections: (a) cardiovascular morbidity effects of acute 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 cardiovascular morbidity effects of acute PM exposure 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 associations of PM exposures with changes in various physiological and/or biochemical measures. The latter studies are particularly important in that they are suggestive of possible mechanisms underlying PM cardiovascular effects.

This section begins with a brief summary of key findings from the 1996 PM AQCD regarding acute cardiovascular effects of PM. Next, key new studies are reviewed in the two categories noted above, i.e., ecologic time-series studies and individual-level studies of physiological measures of cardiac function and/or biochemical measures in blood as they relate to ambient pollution. This is followed by discussion of several issues of importance for interpreting the available data, including identification of potentially susceptible sub-populations, roles of environmental co-factors such as weather and other air pollutants, temporal lags in the relationship between exposure and outcome, and the relative importance of various size-classified PM components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$).

8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air quality Criteria Document

Just two studies were available for review in the 1996 PM AQCD that provided results for acute cardiovascular (CVD) morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time-series design and used standard statistical methods. Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett et al. (1995) reported significant associations between fine particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that: "There is a suggestion of a relationship to heart disease, but the results are based on only two studies, and the estimated effects are smaller than those for other endpoints" (U.S. Environmental Protection Agency, 1996a, p. 12-100). The PM AQCD also stated that acute effects on CVD admissions had been demonstrated for elderly populations (i.e., ≥ 65), but that insufficient data existed to assess relative effects on younger populations.

When viewed alongside the more extensive literature on acute CVD mortality that was available at the time, the evidence from ecologic time-series studies reviewed in the 1996 PM AQCD was consistent with acute health risks of PM being larger for cardiovascular and respiratory causes than for other causes. Given the tendency for end-stage disease states to include both respiratory and cardiovascular impairment, and the associated diagnostic overlap

that often exists, it was not possible on the basis of these studies alone to determine which of the two organ systems, if either, was more critically effected.

8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies

8.3.1.3.1 Acute Hospital Admission Studies

Salient methodological features and results of newly available studies that examine associations between daily measures of ambient PM and daily hospital admissions for cardiovascular disease are summarized in Table 8B-1 (see Appendix 8B). As discussed earlier in Sections 8.1.4 and 8.2.2, many studies since 1996 used GAM with default convergence criteria. Several of those studies have been reanalyzed by original investigators using GAM with more stringent convergence criteria and GLM with parametric smooths, such as natural splines (NS) or penalized splines (PN). Again, since the extent of possible bias in PM effect-size estimates caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here focuses mainly on the studies that either did not use GAM Poisson models or those GAM studies which have been reanalyzed using more stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and hospital admissions or emergency visits that meet these criteria are summarized in Table 8-16, along with a few non-North American studies. Reanalyses studies are indicated in Table 8-16 by indentation of the reference citation to the pertinent short communication in the HEI Special Report (HEI, 2003). The table is organized by first summarizing single-pollutant (PM only) analyses and then multi-pollutant (PM + one or more copollutant) analyses for U.S. and non-U.S. studies.

Of particular importance is the NMMAPS multi-city study (Samet et al., 2000a,b; Zanobetti et al., 2000a), as reanalyzed (Zanobetti and Schwartz, 2003b), which provides evidence for significant PM effects on cardiovascular-related hospital admissions and visits, using a variety of statistical models. These results are supported by another multi-city study (Schwartz, 1999) which, however, has not been reanalyzed with alternative statistical models. Numerous other studies, carried out by individual investigators in a variety of locales, present a more varied picture, especially when gaseous co-pollutants have been analyzed in multipollutant models. Most CVD hospital admissions studies reported to date have used PM_{10} as the main particle measure due to the wide availability of ambient PM_{10} monitoring data. However, results

TABLE 8-16. SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-pollutants						
Samet et al. (2000a,b) 14 Cities	Total CVD admissions ≥ 65 yrs	PM_{10} Means: 24.4-45.3	none	0 day	Default GAM	5.5% (4.7, 6.2)
Zanobetti and Schwartz, (2003b) 14 Cities		PM_{10} Means: 24.4-45.3		0-1 day	Default GAM Strict GAM GLM NS GLM PS	5.9% (5.1-6.7) 4.95% (3.95-5.95) 4.8% (3.55-6.0) 5.0% (4.0-5.95)
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	2 day	Default GAM Default GAM Default GAM	8.9% (0.5-18.0) 4.3% (−1.4-10.4)* 10.5% (2.75-18.9)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	8.0% (−0.3-17.1) 6.2% (−2.0-15.0)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.65% (−2.05-9.7)* 3.0% (−2.7-9.0)*
		$PM_{10-2.5}$: 1 3 (7)			Strict GAM GLM NS	10.2% (2.4-18.6)** 8.1% (0.4-16.4)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	1 day 1 day* 0 day**	Default GAM Default GAM Default GAM	2.9% (−10.8-18.8) 3.2% (−6.5-14.0)* 0.2% (−12.2-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	2.8% (−10.9-18.7) 2.0% (−11.7-17.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.2% (−6.6-14.0)* 2.6% (−7.1-13.3)*
		$PM_{10-2.5}$: 13 (7)			Strict GAM GLM NS	0.1% (−12.4-14.4)** 0.0% (−12.5-14.3)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	0 day 1 day* 0 day**	Default GAM Default GAM Default GAM	9.7% (0.15-20.2) 9.1% (2.4-16.2)* 5.2% (−3.25-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	9.2% (−0.3-19.6) 8.4% (−1.0-18.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	8.0% (1.4-15.0)* 6.8% (0.3-13.8)*
		$PM_{10-2.5}$: 13 (7)			Strict GAM GLM NS	4.4% (−4.0-13.5)** 4.9% (−3.55-14.1)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41 (23)	none	0 day	GAM not used	3.9% (1.0-6.9)

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-pollutants (cont'd)						
Linn et al. (2000) Los Angeles, CA	Total CVD admissions ≥ 30 yrs	PM_{10}: 45 (18)	none	0 day	GAM not used	3.25% (2.04, 4.47)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35‡ (22)	none	0 day	Default GAM	4.2% (3.0, 5.5)
Moolgavkar (2003) Cook County, IL					Strict GAM_{100df} GLM NS_{100df}	4.05% (2.9-5.2) 4.25% (3.0-5.5)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	none	0 day	Default GAM Default GAM	3.2% (1.2, 5.3) 4.3% (2.5, 6.1)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}: 44‡ (26)			Strict GAM_{30df} Strict GAM_{100df} GLM NS_{100df}	3.35% (1.2-5.5) 2.7% (0.6-4.8) 2.75% (0.1-5.4)
		$PM_{2.5}$: 22‡ (16)			Strict GAM_{30df} Strict GAM_{100df} GLM $nspline_{100df}$	3.95% (2.2-5.7)* 2.9% (1.2-4.6)* 3.15% (1.1-5.2)*
Tolbert et al., (2000a) Atlanta, GA 1993-1998	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 1 PM_{10}: 30.1, 12.4	none	0-2 day avg.	GAM not used	−8.2% (p=0.002)
Tolbert et al., (2000a) Atlanta, GA 1998-1999	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 2 PM_{10}: 29.1, 12.0 $PM_{2.5}$: 19.4, 9.4 $PM_{10-2.5}$: 9.4, 4.5	none	0-2 day avg.	GAM not used	5.1% (−7.9, 19.9) 6.1% (−3.1, 16.2)* 17.6% (−4.6, 45.0)**
U.S. Results With Co-pollutants						
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	2 day	Default GAM Default GAM Default GAM	8.5% (-0.45-18.3) 3.7% (-2.4-10.3)* 10.1% (2.25-18.6)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	1 day 1 day 0 day	Default GAM Default GAM Default GAM	−1.3% (−15.5-15.4) 0.55% (−9.7-12.0)* −1.0% (−13.4-13.05)**

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results With Co-pollutants (cont'd)						
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	0 day 1 day 0 day	Default GAM Default GAM Default GAM	7.5% (−2.6-18.7) 8.9% (2.2-16.1)* 3.9% (−4.7-13.2)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41, 23	CO, NO_2, SO_2, O_3	0 day	GAM not used	2% (−1-6)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35, 22	NO_2	0 day	Default GAM	1.8% (0.4, 3.2)
Moolgavkar (2003) Cook County, IL		PM_{10}: 35, 22	CO		Strict GAM_{100df} GLM NS_{100df}	2.95% (1.7-4.2) 3.1% (1.8-4.4)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	CO	0 day	Default GAM Default GAM	−1.8% (−4.4, 0.9) 0.8% (−1.3, 2.9)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}			Strict GAM_{100df} GLM NS_{100df}	−1.3% (−3.8-1.2) −1.1% (-4.2-2.0)
		$PM_{2.5}$			Strict GAM_{100df} GLM NS_{100df}	1.0% (−1.1-3.3)* 1.45% (−1.1-4.0)*
Non-U.S. Results Without Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, 22 $PM_{2.5}$: 17, 15 $PM_{10-2.5}$: 12, 7	none	1-4 day avg.	GAM not used	12.1% (1.4, 23.8) 7.2% (−0.6, 15.6)* 20.5% (8.2, 34.1)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0 $PM_{2.5}$: 8.5, 5.9	none	1-3 day avg.	GAM not used	29.3% (p=0.003) 14.4% (p = 0.055)*
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	none	0 day	GAM not used	2.5% (−0.2, 5.3)
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	none	1-3 day avg.	GAM not used	12.4% (4.6, 20.9)
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	none	0-2 day avg.	GAM not used	4.1% (1.3, 6.9)

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome Measure	Mean PM levels (IQR) in $\mu g/m^3$	Co-pollutants Analyzed with PM	Lag Structure	Method	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} or 25 $\mu g/m^3$ $PM_{2.5}$*, $PM_{10-2.5}$**
Non-U.S. Results With Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, IQR 22	O_3, NO_2, SO_2, CO	1-4 day avg.	GAM not used	−1.4% (−12.5, 11.2)
		$PM_{2.5}$: 17, 15				−1.6% (−10.5, 8.2)*
		$PM_{10-2.5}$: 12, 7				12.1% (−1.9, 28.2)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0	CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur	1-3 day avg.	GAM not used	PM_{10} not significant; no quantitative results presented
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	NO_2, O_3, SO_2, CO	0 day	GAM not used	PM_{10} not significant; no quantitative results presented
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	SO_2, NO_2, O_3, CO	1-3 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	NO_2, O_3, SO_2	0-2 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented

*$PM_{2.5}$ entries, **$PM_{10-2.5}$. All others relate to PM_{10}; ‡Median.

from these studies may also be relevant to an assessment of $PM_{2.5}$ health effects because $PM_{2.5}$ is known to represent 50% or more of PM_{10} in most locations, especially in urban areas typically studied epidemiologically.

A substantial body of new results has emerged from analyses of daily CVD hospital admissions in persons 65 and older in relation to PM_{10} in 14 cities from the NMMAPS multi-city study (Samet et al., 2000a,b). The cities studied included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado Springs, CO; Detroit, MI; Minneapolis/ St. Paul, MN; Nashville, TN; New Haven, CT; Pittsburgh, PA; Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range of years studied encompassed 1985-1994, although this varied by city. Covariates included SO_2, NO_2, O_3, and CO; however these were not analyzed directly as regression covariates. Individual cities were analyzed first by Poisson regression methods on

PM_{10} for lags from 0 to 5 days. An overall PM_{10} risk estimate was then computed by taking the inverse-variance weighted mean of the city-specific risk estimates. The city-specific risk estimates for PM_{10} were also examined for correlations with omitted covariates, including other pollutants. No relationship was observed between city-specific risk estimates and measures of socioeconomic status, including percent living in poverty, percent non-white, and percent with college educations. The overall weighted mean risk estimate for PM_{10} was greatest for lag 0 and for the mean of lags 0-1. For example, the mean risk estimate for the mean of lags 0-1 was a 5.9% increase in CVD admissions per 50 $\mu g/m^3$ PM_{10} (95% CI: 5.1 - 6.7). The mean risk was larger in a subgroup of data where PM_{10} was less than 50 $\mu g/m^3$, suggesting the lack of a threshold. A weakness of this study was its failure to report multipollutant results. The authors argued that confounding by co-pollutants was not present because the city-specific risk estimates did not correlate with city-specific regressions of PM_{10} on co-pollutant levels. However, the validity of this method for identifying meaningful confounding by co-pollutants at the daily time-series level has not been demonstrated. Thus, it is not possible to conclude from these results alone that the observed PM_{10} associations were independent of co-pollutants.

The Samet et al. (2000a,b) reports used GAM LOESS smoothing to control for time and weather covariates. Data from the 14 city NMMAPs analysis of CVD hospital admissions were reanalyzed recently (Zanobetti and Schwartz, 2003b) using three alternative control methods. A small decrease in overall effects was observed as compared with the original study results. Whereas the original 14 city pooled analysis yielded a 5.9% increase in CVD admissions per 50 $\mu g/m^3$ increase in mean lags 0 and 1 day PM_{10} (95% CI: 5.1-6.7%), the reanalysis reported 4.95% (3.95-5.95%), 4.8% (3.55-6.0%), and 5.0 (4.0-5.95%) when reanalyzed by GAM with stringent convergence criteria, GLM with natural spline, and GLM with penalized spline, respectively. On the basis of these results, no change is warranted with regard to the overall conclusions for the original published study.

Zanobetti et al. (2000a) reanalyzed a subset of 10 cities from among the 14 evaluated by Samet et al. (2000a,b). The same basic pattern of results obtained by Samet et al. (2000a,b) were found, with strongest PM_{10} associations on lag 0 day, smaller effects on lag 1 and 2, and none at longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (95% CI 4.7, 6.4) per 50 $\mu g/m^3$ PM_{10} increment. The 0-1 day lag average excess CVD risk = 6.2% (95% CI 5.4, 7.0) per 50 $\mu g/m^3$ PM_{10} increment. Effect-size estimates increased when data were

restricted to days with $PM_{10} < 50$ μg/m^3. As before, no evidence of gaseous (CO, O_3, SO_2) co-pollutant modification of PM effects was seen in the second stage analyses. Again, however, co-pollutants were not tested as independent explanatory variables in the regression analysis. Like the larger NMMAPS morbidity analyses reported by Samet et al. (2000a,b), this sub-study utilized the GAM function in SPlus. These 10 cities were among the 14 cities that Zanobetti and Schwartz (2003b) recently reanalyzed using alternative statistical methods, and the results discussed above would thus apply in general here.

Janssen et al. (2002), in further analyses of the data set examined above by Samet et al. (2000a,b), evaluated whether differences in prevalence 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 in the 14 cities. Cities were characterized and analyzed as either winter or nonwinter peaking for the AC analyses. Data on the prevalence of AC from the 1993 American Housing Survey of the United States Census Bureau (1995) were used to calculate the percentage of homes with central AC for each metropolitan area. Data on PM_{10} emissions by source category were obtained by county from the U.S. EPA emissions and air quality data web site (U.S. Environmental Protection Agency, 2000a). In an analysis of all 14 cities, central AC was not strongly associated with PM_{10} coefficients. However, separate analysis for nonwinter-peaking and winter-peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased significantly with increased percentage of central AC for both groups of cities. There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, suggesting that mobile source particles may have more potent cardiovascular effects than other particle types. For both analyses, similar though weaker, patterns were found for hospitalization for COPD and pneumonia. The authors note that the stronger relationship for hospital admission rates for CVD over COPD and pneumonia may relate to the 10 times higher CVD hospital admissions rate (which would result in a more precise estimate). However, no co-pollutant analyses were reported. The ecologic nature and limited sample size also indicate the need for further study. Because Janssen et al.'s analysis utilized the GAM function in SPlus, Zanobetti et al. (2003b) reanalyzed the main findings from this study using alternative methods for controlling time and weather covariates. While the main conclusions of the study were not significantly altered, some changes in results are worth noting. The effect of air conditioning remained significant for the

non-winter PM_{10}-peaking cities. The significance of highway vehicles and diesels on PM_{10} effect sizes remained significant, as did oil combustion. However, the effect of air conditioning use on PM_{10} effect estimates was less pronounced and no longer statistically significant at $p < 0.05$ for the winter PM_{10}-peaking cities using natural splines or penalized splines, in comparison to the original Janssen et al. GAM analysis.

Schwartz (1999) extended the analytical approach he had used in Tucson (described below) to eight more U.S. metropolitan areas, limiting analyses to a single county in each location to enhance the representativeness of the air pollution data. The locations analyzed were Chicago, IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN; Seattle, WA; Spokane, WA; and Tacoma, WA. Again, the analyses focused on total cardiovascular (CVD) hospital admissions among persons ≥ 65 years old. In univariate regressions, remarkably consistent PM_{10} associations with CVD admissions were found across the eight locations, with a 50 $\mu g/m^3$ increase in PM_{10} associated with 3.6 to 8.6% increases in admissions. The univariate eight-county pooled PM_{10} effect was 5.0% (CI 3.7-6.4), similar to the 6.1 % effect per 50 $\mu g/m^3$ observed in the previous Tucson analysis. In a bivariate model that included CO, the pooled PM_{10} effect size diminished somewhat to 3.8% (CI 2.0-5.5) and the CO association with CVD admissions was generally robust to inclusion of PM_{10} in the model. The Schwartz 1999 paper used GAM LOESS smoothing with default convergence criteria to control for time and weather covariates. To date, no revised results have been reported using alternative statistical methods.

Turning to some examples of independent single-city analyses, PM_{10} associations with CVD hospitalizations were also examined in a study by Schwartz (1997), which analyzed three years of daily data for Tucson, AZ linking total CVD hospital admissions for persons ≥65 years old with PM_{10}, CO, O_3, and NO_2. As was the above case in Chicago, only one site monitored daily PM_{10}, whereas multiple sites did so for gaseous pollutants (O_3, NO_2, CO). Both PM_{10} and CO were independently (i.e., robustly) associated with CVD-related admissions; but O_3 and NO_2 were not. The percent effect of a 50 $\mu g/m^3$ increase in PM_{10} changed only slightly from 6.07 (CI 1.12-11.27) to 5.22 (CI 0.17 - 10.54) when CO was included in the model along with PM_{10}. The Schwartz 1997 paper utilized GAM smoothing to control for time and weather covariates. To date, no revised results have been reported using alternative statistical methods.

Morris and Naumova (1998) reported results for PM_{10}, as well as for O_3, NO_2, and SO_2, in an analysis of four years of congestive heart failure data among people ≥ 65 years old in

Chicago, IL. As many as eight monitoring sites were available for calculating daily gaseous pollutant concentrations; however, only one site in Chicago monitored daily PM_{10}. Only same-day results were presented, based on an initial exploratory analysis showing strongest effects for same-day pollution exposure (i.e., lag 0). Associations between hospitalizations and PM_{10} were observed in univariate regressions (3.9% [1.0, 6.9] per 50 $\mu g/m^3$ PM_{10} increase), but these diminished somewhat in a multi-pollutant model (2.0%, [−1.4, 5.4]). Strong, robust associations were seen between CO and congestive heart failure admissions. These results seem to suggest a more robust association with CO than with PM_{10}. However, the observed differences might also be due in part to differential exposure misclassification for PM_{10} (monitored at one site) as compared with CO (eight sites). This study did not use GAM functions to control for time and weather covariates.

In a study designed to compare the effects of multiple PM indices, Lippmann et al. (2000) analyzed associations between PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ and various categories of CVD hospital admissions among the elderly (65+ yr) in Detroit on 344 days in the period 1992-1994. While no consistent differences were observed in the relative risks for the alternative PM indices, many of the associations involving PM were significant: (a) ischemic heart disease (IHD) in relation to PM indices (i.e., 8.9% [0.5, 18.0] per 50 μg PM_{10}); 10.5% (2.8, 18.9) per 25 $\mu g/m^3$ $PM_{10-2.5}$; and 4.3% (−1.4, 10.4) per 25 $\mu g/m^3$ $PM_{2.5}$ (all at lag 2d); and (b) heart failure (i.e., 9.7% [0.2, 20.2] per 50 $\mu g/m^3$ PM_{10}); 5.2% (−3.3, 14.4) per 25 $\mu g/m^3$ $PM_{10-2.5}$; and 9.1% (2.4, 16.2) per 25 $\mu g/m^3$ $PM_{2.5}$ (the first two at lag 0 d and the latter at lag 1 d). No associations with dysrythmias were seen however. The PM effects generally were robust when co-pollutants were added to the model. Results for 2-pollutant models involving CO are given in Table 8-16 above.

As discussed earlier with regard to the Lippmann et al. (2000) mortality findings, it is difficult to discern whether the observed associations with coarse fraction particles ($PM_{10-2.5}$) are independently due to such particles or may possibly be attributed to the moderately correlated fine particle ($PM_{2.5}$) fraction in Detroit. In addition, power was limited by the small sample size. Because GAM was used in the analyses reported in Lippmann et al. (2000), Ito (2003) has recently reported reanalyses results for the Detroit study using GAM with more stringent convergence criteria and GLM with natural splines. PM effect sizes diminished somewhat (up to 30%) and sometimes lost significance. However, these changes tended to affect all PM metrics in a similar fashion. Thus, there was no change in basic conclusions for the original Lippmann

et al. (2000) study, i.e., that there was no evidence for stronger effects for one size fraction versus others. Ito (2003) also noted that study results were more sensitive to alternative weather models and degree of smoothing (degrees of freedom used for the smoothing function) than to whether or not GAM, with strict convergence criteria, was used.

As part of the ARIES Study, Tolbert et al. (2000a) initially reported preliminary results for multiple PM indices as they relate to daily hospital emergency department (ED) visits for dysrhythmias (DYS) and all CVD categories for persons aged 16 yrs or older, based on analyses of data from 18 of 33 participating hospitals in Atlanta, GA. During Period 1 of the study (1993-1998), PM_{10} from the EPA AIRS database was reported to be negatively associated with CVD visits. In a subsequent one-year period (Aug. 1998-Aug. 1999), when data became available from the Atlanta PM supersite, positive but non-significant associations were seen between CVD and PM_{10} (RR of 5.1% per 50 $\mu g/m^3$ PM_{10}) and $PM_{2.5}$ (RR of 6.1% per 25 $\mu g/m^3$ $PM_{2.5}$); and significant positive associations were seen with certain fine particle components, i.e., elemental carbon ($p \leq 0.005$) and organic carbon ($p \leq 0.02$), and CO ($p \leq 0.005$). No multi-pollutant results were reported. Study power was limited due to the short data record in Period 2. More complete analyses for January 1993 to August 2000 data from all participating hospitals have recently been reported (Metzger et al., 2003) to show that, using an a priori 3-day morning average in single-pollutant GLM analyses, CVD visits were associated with $PM_{2.5}$, organic carbon, elemental carbon, oxygenated hydrocarbons, CO, and NO_2 (but not with O_3 or SO_2). Secondary analyses suggested that these associations were strongest for same day air pollutant levels.

In an analysis of 1992-1995 Los Angeles data, Linn et al. (2000) also found that PM_{10}, CO, and NO_2 were all significantly associated with increased CVD admissions in single-pollutant models among persons aged 30 yr and older. Associations generally appeared to be stronger for CO than for PM_{10}. No PM_{10} results were presented with co-pollutants in the model. Neither Tolbert et al. nor Linn et al. reported any key findings based on GAM analyses.

Lastly, Moolgavkar (2000b) analyzed PM_{10}, CO, NO_2, O_3, SO_2 and limited $PM_{2.5}$ data in relation to daily total cardiovascular (CVD) and total cerebrovascular (CrD) admissions for persons aged $\geq$65 from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ) in the period 1987-1995. Of particular note was the availability of $PM_{2.5}$ data in LA, though only every sixth day. Consistent with most studies, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) were

associated at some lags with CVD admissions in Cook and LA counties, but not in Maricopa county. However, in two-pollutant models in Cook and LA counties, the PM risk estimates diminished substantially and/or were rendered non-significant, whereas co-pollutant (CO or NO_2) risk estimates were less affected. These results suggest that gaseous pollutants, with the exception of O_3, may have been more strongly associated with CVD hospitalizations than was PM. These findings were based on an analysis that used GAM functions for time and weather controls. Moolgavkar (2003) reported results of a reanalysis using improved GAM convergence criteria and GLM with natural splines (nspline) and a range of degrees of freedom (30 versus 100) for the smooth function of time. Results were not very sensitive to the use of default versus improved GAM or splines (Table 8-16) but did appear to be more sensitive to degrees of freedom. The nspline results were given only with 100 degrees of freedom. This is an unusually large number, especially for $PM_{2.5}$, where data were available only every sixth day over a nine year period.

The above analyses of daily PM_{10} and CO in U.S. cities, overall, indicate that elevated concentrations of both PM_{10} and CO may enhance risk of CVD-related morbidity leading to increased ED visits or hospitalizations. The Lippmann results appear to implicate both $PM_{2.5}$ and $PM_{10-2.5}$ in increased hospital admissions for some categories of CVD among the elderly.

8.3.1.3.2 Studies in Non-U.S. Cities

Four separate analyses of hospitalization data in Canada have been reported by Burnett and coworkers since 1995 (Burnett et al., 1995, 1997a,c, 1999). A variety of locations, outcomes, PM exposure metrics, and analytical approaches were used, which hinders somewhat the ability to draw broad conclusions across the full group of studies. The first study (Burnett et al., 1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in Ontario, CN. Respiratory and CVD hospital admissions were analyzed in relation to sulfate and O_3 concentrations. Sulfate lagged one day was associated with CVD admissions, with an effect of 2.8% (CI 1.8-3.8) increase per 13 $\mu g/m^3$ SO_4^{-2} without O_3 in the model and 3.3% (CI 1.7-4.8) with O_3 included. When CVD admissions were split out into sub-categories, larger associations were seen between sulfates and coronary artery disease and heart failure than for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the elderly $\geq$ 65 yr old

(3.5% per 13 μg/m^3) than for those < 65 yr old (2.5% per 13 μg/m^3). There was little evidence for seasonal differences in sulfate associations.

Burnett et al. (1997c) analyzed daily congestive heart failure hospitalizations in relation to CO and other air pollutants (O_3, NO_2, SO_2, CoH) in ten large Canadian cities as a replication of an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study expanded upon the previous work both by its size (11 years of data for each of 10 large cities) and by including a measure of PM air pollution (coefficient of haze, CoH); whereas no PM data were included in the earlier Morris et al. study. The Burnett study was restricted to the population ≥ 65 years old. The authors noted that all pollutants except O_3 were correlated, making it difficult to separate them statistically. CoH, CO, and NO_2 measured on the same day as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in univariate models. In multi-pollutant models, CO remained a strong predictor, but CoH did not (no gravimetric PM measures were used).

The roles played by size-selected gravimetric and chemically-speciated particle metrics as predictors of CVD hospitalizations were explored in analyses of data from metropolitan Toronto for the summers of 1992-1994 (Burnett et al., 1997a). The analyses used dichotomous sampler ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$), hydrogen ion, and sulfate data collected at a central site as well as O_3, NO_2, SO_2, CO, and CoH data collected at multiple sites in Toronto. Hospital admissions categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac dysrhythmias, and heart failure) and total respiratory-related admissions. Model specification with respect to pollution lags was completely data-driven, with all lags and averaging times out to 4 days prior to admission evaluated in exploratory analyses and "best" metrics chosen on the basis of maximal t-statistics. The relative risks of CVD admissions were positive and generally statistically significant for all pollutants analyzed in univariate regressions, but especially so for O_3, NO_2, CoH, and $PM_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants were generally robust to inclusion of PM covariates, whereas the PM indices (aside from CoH) were not robust to inclusion of multiple gaseous pollutants. In particular, $PM_{2.5}$ was not a robust predictor of CVD admissions in multi-pollutant models: whereas an 25 μg/m^3 increase in $PM_{2.5}$ was associated with a 7.2% increase (t = 1.8) in CVD admissions in a univariate model, the effect was reduced to –1.6% (t = 0.3) in a model that included O_3, NO_2, and SO_2. CoH, like CO and NO_2, is generally thought of as a measure of primary motor-vehicle emissions during the

non-heating season. The authors concluded that "particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this study beyond that attributable to climate and gaseous air pollution."

Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease. The analyses also examined several respiratory causes, as well as cerebrovascular and diseases of the peripheral circulation; the latter categories were included because they should show PM associations if one mechanism of PM action is related to increased plasma viscosity, as suggested by Peters et al. (1997a). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ estimated from daily TSP and TSP sulfate data, based on a regression analysis for dichotomous sampling data that were available every sixth day during an eight-year subset of the full study period. This use of estimated rather than measured PM components limits interpretation of the reported PM results, i.e., in general, use of estimated PM exposure metrics should tend to increase exposure measurement error and thereby tend to decrease effects estimates. Model specification for lags was again data-driven, based on maximal t-statistics. Although some statistically significant associations with one or another PM metric were found in univariate models, there were no significant PM associations with any of the three CVD hospitalization outcomes in multi-pollutant models. For example, whereas an 25 $\mu g/m^3$ increase in estimated $PM_{2.5}$ was associated with a 8.05% increase (t-statistic = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$ association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in the model. The gaseous pollutants dominated most regressions. There also were no associations between PM and cerebral or peripheral vascular disease admissions.

The Burnett et al. studies provide some of the most extensive results for PM in conjunction with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the various analyses confuses the picture. A general finding appears to be lack of robustness of associations between cardiovascular outcomes and PM in multi-pollutant analyses. This was seen for CoH in the analysis of 10 Canadian cities (Burnett et al., 1997c), for $PM_{2.5}$ and PM_{10} in the analysis of summer data in Toronto (Burnett et al., 1997a), and for linear combinations of TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in

Toronto (Burnett et al., 1999). One exception was the association reported between CVD admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the sulfate association was robust to the inclusion of O_3. Also, although gravimetric PM variables were not robust predictors in the Toronto summer analysis, CoH was (Burnett et al., 1997a), perhaps reflecting the influence of primary motor vehicle emissions. This contrasts, however, with CoH's lack of robustness in the 10-city analysis (Burnett et al., 1997c).

Stieb et al. studied all-age acute cardiac emergency room visits in relation to a rich set of pollution covariates in Saint John, Canada for the period 1992-1996. Daily data were available on $PM_{2.5}$, PM_{10}, fine fraction hydrogen and sulfate ions, CoH, CO, H_2S, NO_2, O_3, SO_2, and total reduced sulfur. In a multi-pollutant model, neither PM_{10} nor $PM_{2.5}$ were significantly related to total cardiac ED visits, though O_3 and SO_2 were.

The APHEA II (Le Tertre et al., 2002) project examined the association between PM_{10} and hospital admissions for cardiac causes in eight European cities. They found a significant effect of PM_{10} (0.5%; 0.2, 0.8) on admission for cardiac causes (all ages) and cardiac causes (0.7%; 0.4, 1.0) and ischemic heart disease (0.8%; 0.3, 1.2) for people over 65 years, with the effect 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 PM_{10} effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. In contrast to PM_{10}, black smoke was robustly associated with CVD hospital admissions when co-pollutants were introduced into the model. This led the authors to suggest that diesel PM may be especially important. GAM functions were used in the original analysis. In a recent reanalysis using GAM with stringent convergence criteria and GLM with either natural or penalized splines, no marked changes from original results were observed (Le Tertre et al., 2003).

Several additional non-U.S. studies, mainly in the U.K., have also been published since the 1996 PM AQCD. Most of these studies evaluated co-pollutant effects along with those of PM. Interpretation is hindered somewhat, however, by the failure to report quantitative results for PM_{10} in the presence of co-pollutants. In univariate models, Atkinson et al. (1999b) reported PM associations for persons aged < 65 yr and for persons aged ≥ 65 yr. Significant associations were reported for both ambient PM_{10} and black smoke (BS), as well as all other co-pollutants, with daily admissions for total cardiovascular disease and ischemic heart disease for 1992-1994 in London, UK, using standard time-series regression methods. In two-pollutant models, the

associations with PM_{10}, NO_2, SO_2, and CO were moderated by the presence of BS in the model, but the BS association was robust to co-pollutants. Interpretation is hampered somewhat by the lack of quantitative results for two-pollutant models.

In another U.K. study, associations with PM_{10}, and to a lesser extent BS, SO_2, and CO, were reported for analyses of daily emergency hospital admissions for cardiovascular diseases from 1992-1995 for Edinburgh, UK (Prescott et al., 1998). No associations were observed for NO_2 and O_3. Significant PM_{10} associations for CVD admissions were present only in persons < 65 yrs old. The authors reported that the PM_{10} associations were unaffected by inclusion of other pollutants; however, results were not shown. On the other hand, no associations between PM_{10} and daily ischemic heart disease admissions were observed by Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK. However, PM_{10} was associated with respiratory admissions and cardiovascular mortality during the same study period. This inconsistency of results across causes and outcomes is difficult to interpret, but may relate in part to the relatively short time-series analyzed. The authors stated that gaseous pollutants did not have significant associations with health outcomes independent of PM, but no results were presented for models involving gaseous pollutants.

A study in Hong Kong by Wong et al. (1999a) found associations between CVD admissions and PM_{10}, SO_2, NO_2, and O_3 in univariate models, but did not examine multi-pollutant models. In models including PM_{10} and dichotomous variables for gaseous pollutants (high versus low concentration), the PM_{10} effects remained relatively stable. Ye and colleagues analyzed a 16 year record of daily emergency hospital visits for July and August in Tokyo among persons age 65 and older (Ye et al., 2001). In addition to PM_{10}, the study included NO_2, O_3, SO_2, and CO. Models were built using an objective significance criterion for variable inclusion. NO_2 was the only pollutant significantly associated with angina, cardiac insufficiency, and myocardial infarction hospital visits.

8.3.1.3.3 Summary of Salient Findings for Acute PM Exposure Effects on CVD Hospital Admissions

The ecologic time-series studies reviewed here add substantially to the body of evidence on acute CVD morbidity effects of PM and co-pollutants. Two U.S. multi-city studies offer the strongest current evidence for effects of PM_{10} on acute CVD hospital admissions, but uncertainties regarding the possible role of co-pollutants in the larger of the two studies hinders

interpretation with respect to independent PM_{10} effects. Among single-city studies carried out in the U.S. and elsewhere by a variety of investigators (see Table 8-16), less consistent evidence for PM effects is seen. Of particular importance is the possible roles of co-pollutants (e.g., CO) as confounders of the PM effect. Among 13 independent studies that included gravimetrically-measured PM_{10} and co-pollutants, three reported PM effects that appeared to be independent of co-pollutants (Schwartz, 1997; Lippmann et al., 2000; Prescott et al., 1998); eight reported no significant PM_{10} effects after inclusion of co-pollutants (Morris and Naumova, 1998; Moolgavkar, 2000b; Tolbert et al., 2000a; Burnett et al., 1997a; Steib et al., 2000; Atkinson et al., 1999b; Wordley et al. (1997); Morgan et al., 1998; Ye et al., 2001); and two studies were unclear regarding independent PM effects (Linn et al., 2000; Wong et al., 1999a). In a recent quantitative review of published results from 12 studies on airborne particles and hospital admissions for cardiovascular disease, Morris (2001) noted that adjustment for co-pollutants consistently reduced the PM_{10} effect, with reductions ranging from 10 to 320% across studies. Thus, although several studies do appear to provide evidence for PM effects on CVD hospital admissions independent of co-pollutant effects, a number of other studies examining co-pollutants did not find results indicative of independent PM_{10} effects on CVD hospital admissions

With respect to particle size, only a handful of studies have examined the relative effects of different particle indicators (Lippmann et al., 2000; Burnett et al., 1997a; Tolbert et al., 2000a; Steib et al., 2000; Moolgavkar, 2000b). Perhaps due to statistical power issues, no clear picture has emerged as to particle-size fraction(s) most associated with acute CVD effects.

As discussed above, several studies originally based on statistical analyses involving the SPlus GAM function have reported new results using alternative statistical methods. The reanalyses yielded some slightly reduced effect estimates and/or increased confidence intervals or little or no change resulted in other cases. Thus, based on these new results, the overall conclusions from the cardiovascular hospitalization studies remain the same.

Because hospitalization can be viewed as likely reflecting some of the same pathophysiologic mechanisms that may be responsible for acute mortality following PM exposure, it is of interest to assess the coherence between the morbidity results reviewed here and the mortality results reviewed in Section 8.2.2 (Borja-Aburto et al., 1997, 1998; Braga et al., 2001; Goldberg et al., 2000; Gouveia and Fletcher, 2000; Hoek et al., 2001; Kwon et al., 2001;

Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson et al., 1997; Wordley et al., 1997; Zeghnoun et al., 2001; Zmirou et al., 1998). The mortality studies reported significant associations between acute CVD mortality and measures of ambient PM, though the PM metrics used and the relative risk estimates obtained varied across studies. The PM measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and black smoke (filter reflectance). Where tested, PM associations with acute CVD mortality appeared to be generally more robust to inclusion of gaseous covariates than was the case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998; Wordley et al., 1997; Zmirou et al., 1998). One study (Goldberg et al., 2000) which examined multiple alternative PM metrics, reported strongest associations with $PM_{2.5}$ and no associations for $PM_{10-2.5}$ and hydrogen ion. Three studies (Braga et al., 2001; Goldberg et al., 2000; Hoek et al., 2001), as noted in Section 8.2.2, provide data indicating that some specific CVD causes of mortality (such as heart failure) were more strongly associated with air pollution than total CVD mortality; but it was noted that ischemic heart disease (which contributes about half of all CVD deaths) was the strongest contributor to the association between air pollution and cardiovascular mortality. Checkoway et al. (2000) evaluated the possible association between the occurrence of out-of-hospital sudden cardiac arrest (SCA) for cases free of prior clinically-recognized heart disease or major life-threatening co-morbidity and daily PM levels in Seattle (PM_{10} mean = 31.9 $\mu g/m^3$) and reported an estimated relative risk at a one day lag of 0.87 (95% CI: 0.74, 1.01). The above-noted results for acute CVD mortality are qualitatively consistent with those reviewed earlier in this section for hospital admissions.

Figure 8-12 illustrates PM_{10} excess risk estimates for single-pollutant models derived from selected U.S. studies of PM_{10} exposure and total CVD hospital admissions, standardized to a 50 $\mu g/m^3$ exposure to PM_{10} as shown in Table 8-16. Results are shown both for studies yielding pooled outcomes for multiple U.S. cities and for studies of single U.S. cities. The Zanobetti and Schwartz (2003b) and Samet et al. (2000a) pooled cross-city results for 14 U.S. cities provide the most precise estimate for relationships of U.S. ambient PM_{10} exposure to increased risk for CVD hospitalization. That estimate, and those derived from most other studies depicted in Figure 8-12, generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of 3-9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 yr).

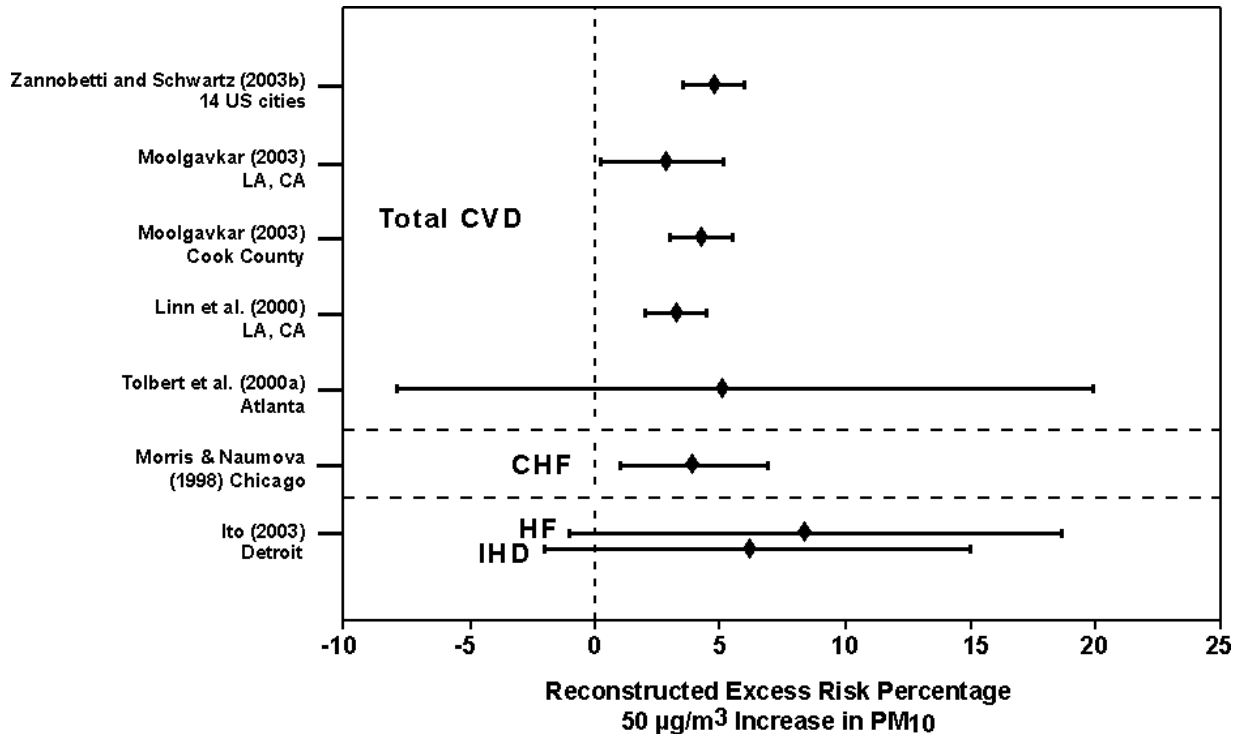

Figure 8-12. Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from selected U.S. PM_{10} studies based on single-pollutant models. Both multi-pollutant models and $PM_{2.5}$ and $PM_{10-2.5}$ results are shown in Table 8-16. CVD = cardiovascular disease. CHF = congestive heart failure, HF = heart failure.

Other individual-city results (see Table 8-16) from Detroit are also indicative of excess risk for ischemic heart disease in the range of approximately 3.0 and 8.1% per 25 µg/m^3 of $PM_{2.5}$ or $PM_{10-2.5}$, respectively, and for heart failure of 6.8% and 4.9% excess risk per 25 µg/m^3 of $PM_{2.5}$ and $PM_{10-2.5}$, respectively. However, the extent to which PM affects CVD-hospitalization risks independently of, or together with other co-pollutants (such as CO), remains to be further resolved.

8.3.1.3.4 Individual-Level Studies of Cardiovascular Physiology

Several new studies have evaluated longitudinal associations between ambient PM and physiologic measures of cardiovascular function or biochemical changes in the blood that may be associated with *cardiac risks*. In contrast to the ecologic time-series studies discussed above,

these studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions regarding individual risks, as well as to explore mechanistic hypotheses. Heterogeneity of responses across individuals, and across subgroups defined on the basis of age, sex, pre-existing health status, etc., also can be assessed, in principle. While exposure assessment remains largely ecologic (i.e., the entire population is usually assigned the same exposure value on a given day), exposure is generally well characterized in the small, spatially-clustered study populations. The recent studies fall into two broad classes: (1) those addressing cardiac rhythm or adverse events and (2) those addressing blood characteristics. While significant uncertainty still exists regarding the interpretation of results from these new studies, the varied responses that have been reported to be associated with ambient PM and co-pollutants are of much interest in regard to mechanistic hypotheses concerning pathophysiologic processes potentially underlying CVD-related mortality/morbidity effects discussed in preceding sections.

Cardiac Physiology and Adverse Cardiac Events

Alterations in heart rate and/or rhythm have been hypothesized as possible mechanisms by which ambient PM exposures may exert acute effects on human health. Decreased heart rate variability, in particular, has been identified as a predictor of increased cardiovascular morbidity and mortality. Several independent studies have recently reported temporal associations between PM exposures and various measures of heart beat rhythm in panels of elderly subjects (Liao et al., 1999; Pope et al., 1999a,b,c; Dockery et al., 1999; Peters et al., 1999a, 2000a; Gold et al. 2000; Creason et al., 2001). Changes in blood pressure may also reflect increases in CVD risks (Linn et al., 1999; Ibald-Mulli et al., 2001). Finally, one important new study (Peters et al., 2001a) has linked acute (2- and 24-h) ambient $PM_{2.5}$ and PM_{10} concentrations with increased risk of myocardial infarction in subsequent hours and days.

Liao et al. (1999) studied 26 elderly subjects (age 65-89 years; 73% female) over three consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were classified as "compromised" based on previous cardiovascular conditions (e.g., hypertension). Daily six-minute resting electrocardiogram (ECG) data were collected, and time intervals between sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval data to separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N–N; also

designated R-R) heartbeat intervals (SDNN) was computed as a time-domain outcome variable. $PM_{2.5}$ was monitored indoors by TEOM and outdoors by dichotomous sampler. Outdoor $PM_{2.5}$ levels ranged from 8.0 to 32.2 $\mu g/m^3$ (mean = 16.1 $\mu g/m^3$). Regression analyses controlled for inter-subject differences in average variability, allowing each subject to serve as his/her own control. Consistent associations were seen between decreases in all three outcome variables (LF, HF, SDNN) and increases in $PM_{2.5}$ levels (both indoors and outdoors), with associations being stronger for the 18 "compromised" subjects. No analyses of heart rate were reported.

Creason et al. (2001) reported results of a subsequent study using similar methods among 56 elderly residents of a retirement center in Baltimore County, MD. The 11 men and 45 women ranged in age from 72 to 97 years and were all Caucasian. Associations between decreased HRV and ambient $PM_{2.5}$ were again seen, though not significant at $p < 0.05$ level and smaller than in the previous Baltimore study. When two episodic $PM_{2.5}$ days with rainfall were excluded from the 24-day data set, the $PM_{2.5}$ associations increased in magnitude and became statistically significant. There was no evidence of larger effects among subsets of subjects with compromised health status. No results were presented for other pollutants besides $PM_{2.5}$.

Pope and colleagues (1999c) reported similar findings in a panel of six elderly subjects (69-89 years, 5/6 male) with histories of cardiopulmonary disease, and one 23-year old male subject suffering from Crohn's disease and arrhythmias. Subjects carried Holter monitors for up to 48 hours during different weeks that varied in ambient PM_{10} concentrations. N-N heartbeat intervals were recorded to calculate several measures of heart rate variability in the time domain: the standard deviation of N-N intervals (SDNN), a broad measure of both high and low frequency variations; the standard deviation of the averages of N-N intervals in all five minute segments (SDANN), a measure of ultra-low frequency variations; and the root mean squared differences between adjacent N-N intervals (r-MSSD), a measure of high frequency variations. Daily gravimetric PM_{10} data obtained from three sites in the study area ranged from circa 10 $\mu g/m^3$ to 130 $\mu g/m^3$ during the study. A simple step function in PM concentration was observed, with high levels occurring only during the first half of the 1.5 month study period. Regression analysis with subject-specific intercepts was performed, with and without control for daily barometric pressure and mean heart rate. Same-day, previous-day, and the two-day mean of PM_{10} were considered. SDNN and SDANN were negatively associated with both same-day and previous-day ambient PM_{10}, and results were unaffected by inclusion of covariates. Heart

rate, as well as r-MSSD, were both positively, but less strongly, associated with PM_{10}. No co-pollutants were studied.

The Pope et al. (1999c) study discussed above was nested within a larger cohort of 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in oxygen saturation might occur as a result of PM exposure, and that this could be a risk factor for adverse cardiac outcomes. The study was carried out in winter months (mid-November through mid-March), when frequent inversions lead to fine particle episodes. PM_{10} levels at the three nearest sites averaged from 35 to 43 $\mu g/m^3$ during the study, and daily 24-h levels ranged from 5 to 147 $\mu g/m^3$. Two populations were studied: 52 retired Brigham Young University faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO_2) and heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger. In regression analyses controlling for inter-individual differences in mean levels, SpO_2 was not associated with PM_{10}, but was highly associated with barometric pressure. In contrast, HR association with PM_{10} significantly increased but significantly decreased with barometric pressure in joint regressions. Including CO in the regressions did not change these basic findings. This was the first study of this type to examine the interrelationships among physiologic measures (i.e., SpO_2 and HR), barometric pressure, and PM_{10}. The profound physiological effects of barometric pressure noted here highlight the importance of carefully controlling for barometric pressure effects in studies of cardiac physiology.

Gold and colleagues (2000) obtained somewhat different results in a study of heart rate variability among 21 active elderly subjects, aged 53-87 yr, in a Boston residential community. Resting, standing, exercising, and recovering ECG measurements were performed weekly using a standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for definitions). Heart rate also was analyzed as an outcome. Continuous PM_{10} and $PM_{2.5}$ monitoring was conducted by TEOM at a site 6 km from the study site and PM data were corrected for the loss of semivolatile mass. Data on CO, O_3, NO_2, SO_2, temperature and relative humidity were available from nearby sites. Outcomes were regressed on $PM_{2.5}$ levels in the 0-24 hour period prior to ECG testing, with and without control for HR and temperature. As for the other studies discussed above, declines in SDNN were associated with $PM_{2.5}$ levels, in this

case averaged over 4 hours. These associations reached statistical significance at the $p < 0.05$ level only when all testing periods (i.e., resting, standing, exercise) were combined. In contrast to the above studies, both HR and r-MSSD here were negatively associated with $PM_{2.5}$ levels (i.e., lower HR and r-MSSD) when $PM_{2.5}$ was elevated. These associations were statistically significant overall, as well as for several of the individual testing periods, and were unaffected by covariate control. Gold et al. (2003) has recently reported revised results that involve analyzing temperature with either a GAM function with stringent convergence criteria or a GLM with natural splines, with no substantial changes being reported.

Further evidence for decreased HRV in response to $PM_{2.5}$ exposures comes from several recent studies. Significant decreases in SDNN of 1.4% (95% CI = 2.1 to −0.6) per 100 ug/m^3 3-hour mean $PM_{2.5}$ were found in a group of young healthy boilermakers in the Boston area who were studied during non-work periods (Magari et al., 2001). Use of estimated $PM_{2.5}$ based on light scattering precludes a firm quantitative interpretation of exposure levels in terms of gravimetric $PM_{2.5}$ concentrations. A previous study of 40 boilermakers (including the 20 studied above) analyzed data collected during both work and non-work time periods (Magari et al., 2002). That study reported a significant 2.7% decrease in SDNN and a 1.0% increase in HR, for every 100 µg/m^3 increase in 4-hour moving average estimated $PM_{2.5}$. The larger effect size for the non-work PM exposure study may reflect differing health effects of ambient versus occupational PM composition. These studies are important in showing HRV effects in young healthy adults.

Peters et al. (1999a) reported HR results from a retrospective analysis of data collected as part of the MONICA study (monitoring of trends and determinants in cardiovascular disease) carried out in Augsburg, Germany. Analyses focused on 2,681 men and women aged 25-64 years who had valid ECG measurements taken in winter 1984-1985 and again in winter 1987-1988. Ambient pollution variables included TSP, SO_2, and CO. The earlier winter included a 10-day episode with unusually high levels of SO_2 and TSP, but not of CO. Pollution effects were analyzed in two ways: dichotomously comparing the episode and non-episode periods, and continuously using regression analysis. However, it is unclear from the report as to what extent the analyses reflect between-subject versus within-subject effects. A statistically significant increase in mean heart rate was seen during the episode period versus other periods, controlling

for cardiovascular risk factors and meteorology. Larger effects were observed in women. In single-pollutant regression analyses, all three pollutants were associated with increased HR.

In another retrospective study, Peters and colleagues (2000a) examined incidence of cardiac arrhythmias among 100 patients (mean age 62.2 yr.; 79% male) with implanted cardioverter defibrillators followed over a three year period. $PM_{2.5}$ and PM_{10} were measured in South Boston by the TEOM method, along with black carbon, O_3, CO, temperature and relative humidity; SO_2 and NO_2 data were obtained from another site. The 5^{th} percentile, mean, and 95^{th} percentiles of PM_{10} levels were 7.8, 19.3, and 37.0 $\mu g/m^3$, respectively. The corresponding $PM_{2.5}$ values were 4.6, 12.7, and 26.6 $\mu g/m^3$. Logistic regression was used to analyze events in relation to pollution variables, controlling for between-person differences, seasons, day-of-week, and meteorology in two subgroups: 33 subjects with at least one arrhythmia event and 6 subjects with 10 or more such events. In the larger subgroup, only NO_2 on the previous day, and the mean NO_2 over five days, were significantly associated with arrhythmia incidence. In patients with 10 or more events, the NO_2 associations were stronger. Also, some of the $PM_{2.5}$ and CO lags became significant in this subgroup.

Linn et al. (1999) reported associations between both diastolic and systolic blood pressure and PM_{10} in a panel study of 30 Los Angeles residents with severe COPD. Recently, Ibald-Mulli et al. (2001) reported similar findings from a study of blood pressure among 2607 men and women aged 25-64 years in the MONICA study in Augsburg, Germany. Systolic blood pressure increased on average during an episode of elevated TSP and SO_2, but the effect disappeared after controlling for meteorological parameters that included temperature and barometric pressure. However, when TSP and SO_2 were analyzed as continuous variables, both were associated with elevated systolic blood pressure, controlling for meteorological variables. In two-pollutant models, TSP was more robust than SO_2. Further, the TSP association was greater in the subgroups of subjects with elevated blood viscosity and heart rates.

An exploratory study of a panel of COPD patients (Brauer et al., 2001) examined several PM indicators in relation to CVD and respiratory health effects. The very low levels of ambient particles (PM_{10} mean = 19 $\mu g/m^3$) and low variability in these levels plus the sample size of 16 limit the conclusions that can be drawn. Nevertheless, for cardiovascular endpoints, single-pollutant models indicated that both systolic and diastolic BP decreased with increasing exposure, but this is not statistically significant. The size of the ambient PM_{10} effect estimate for

ΔFEV_1 was larger than the effect estimate for ambient $PM_{2.5}$ and personal $PM_{2.5}$ but not statistically significant. This initial effort indicates that ambient PM_{10} consistently had the largest effect estimates while models using personal exposure measurements did not show larger or more consistently positive effect estimates relative to those using ambient exposure metrics.

An important study by Peters et al. (2001a) reported associations between onset of myocardial infarction (MI) and ambient PM (either PM_{10} or $PM_{2.5}$) as studied in a cohort of 772 MI patients in Boston, MA. Precise information on the timing of the MI, obtained from patient interviews, was linked with concurrent air quality data measured at a single Boston site. A case crossover design enabled each subject to serve as his/her own control. One strength of this study was its analysis of multiple PM indices and co-pollutants, including real-time $PM_{2.5}$, PM_{10}, the $PM_{10-2.5}$ difference, black carbon, O_3, CO, NO_2, and SO_2. Only $PM_{2.5}$ and PM_{10} were significantly associated with MI risk in models adjusting for season, meteorological parameters, and day of week. Both the mean $PM_{2.5}$ concentration in the previous two hours and in the 24 hours lagged one day were independently associated with MI, with odds ratios of 1.48 (1.09-2.02) for 25 ug/m^3 and 1.62 (1.13-2.34) for 20 ug/m^3, respectively. PM_{10} associations were similar. The non-significant findings for other pollution metrics should be interpreted in the context of potentially differing exposure misclassification errors associated with the single monitoring site.

The above studies present a range of findings suggesting possible effects of $PM_{2.5}$ on cardiac rhythm and adverse events. Numerous studies reported decreases in HR variability associated with PM in elderly subjects with preexisting cardiopulmonary disease, although r-MSSD (a measure of high-frequency HR variability) showed elevations with PM in one study (Pope et al., 1999a). Recent studies also reported effects in healthy elderly and young adult populations. All of the studies which examined HR also found an association with PM; most reported positive associations, but one (Gold et al., 2000) reported a negative relationship. However, variations in methods and results across the studies argue for caution in drawing strong conclusions regarding PM effects from them.

Viscosity and Other Blood Characteristics

Peters et al. (1997a) state that plasma viscosity, a risk factor for ischemic heart disease, is affected by fibrinogen and other large asymmetrical plasma proteins, e.g., immunoglobulin M

and $\propto_2$-macroglobulin. They note that, in a cohort study of elderly men and women, fibrinogen levels were strongly related to inflammatory markers (e.g., neutrophil count and acute-phase proteins, [C-reactive protein and $\propto_1$-antichymotrypsin] and self-reported infections.

Support for a mechanistic hypothesis, relating to enhanced blood viscosity, is suggested in an analysis of plasma viscosity data collected in a population of 3256 German adults in the MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October 1984 to June 1985. An episode of unusually high air pollution levels occurred during a 13 day period while these measurements were being made. Among the 324 persons who provided blood during the episode, there was a statistically significant elevation in plasma viscosity as compared with 2932 persons studied at other times. The odds ratio for plasma viscosity exceeding the 95th percentile was 3.6 (CI 1.6–8.1) among men and 2.3 (CI 1.0–5.3) among women. Analysis of the distribution of blood viscosity data suggested that these findings were driven by changes in the upper tail of the distribution rather than by a general shift in mean viscosity, consistent with the likelihood of a susceptible sub-population.

A prospective cohort study of a subset of male participants from the above-described Augsburg, Germany MONICA study was reported by Peters et al. (2001b). Based on a survey conducted in 1984/85, a sample of 631 randomly selected men (aged 45-64 yr and free of cardiovascular disease at entry) were evaluated in a 3-yr follow-up that examined relationships of air pollution to serum C-reactive protein concentrations. C-reactive protein is a sensitive marker of inflammation, tissue damage, and infections, with acute and chronic infections being related to coronary events. Inflammation is also related to systemic hypercoagulability and onset of acute ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and other areas of Germany, the odds of abnormal increases in serum C-reactive protein (i.e., $\geq$90th percentile of pre-episode levels = 5.7 mg/L) tripled; and associated increases in TSP levels of 26 $\mu g/m^3$ (5-day averages) were associated with an odds ratio of 1.37 (95% CI 1.08-1.73) for C-reactive protein levels exceeding the 90th percentile levels in two pollutant models that included SO_2 levels. The estimated odds ratio for a 30 $\mu g/m^3$ increase in the 5-day mean for SO_2 was 1.12 (95% CI 0.92 = 1.47).

Two other recent studies also examined blood indices in relation to PM pollution (Seaton et al., 1999; Prescott et al., 1999). Seaton and colleagues collected sequential blood samples (up to 12) over an 18 month period in 112 subjects (all over age 60) in Belfast and Edinburgh,

UK. Blood samples were analyzed for hemoglobin, packed cell volumes, fibrinogen, blood counts, factor VII, interleuken 6, and C-reactive protein. In a subset of 60 subjects, plasma albumin also was measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city. Personal exposure estimates for three days preceding each blood draw were derived from ambient data adjusted by time-activity patterns and I/O penetration factors.

No co-pollutants were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons, temperature, and between-subject differences. Significant changes in several blood indices were associated with either ambient or estimated personal PM_{10} levels. All changes were negative, except for C reactive protein in relation to ambient PM_{10}. Prescott et al. (1999) also investigated factors that might increase susceptibility to PM exposure cardiovascular events for a cohort of 1,592 subjects aged 55-74 in Edinburgh, UK, baseline measurements of blood fibrinogen and blood and plasma viscosity were examined as modifiers of PM effects (indexed by BS) on the incidence of fatal and non-fatal myocardial infarction or stroke. All three blood indices were strong predictors of increased cardiac event risk; but there was no clear evidence of either a main effect of BS, nor interactions between BS and blood indices.

Two more new studies examined air pollution associations with plasma fibrinogen. One by Pekkanen and colleagues (2000) analyzed plasma fibrinogen data from a cross-sectional survey of 4,982 male and 2,223 female office workers in relation to same-day and previous three-day PM_{10}, black smoke, NO_2, CO, SO_2, and O_3 concentrations. In the full analysis, NO_2 and CO were significantly associated with fibrinogen levels. When the analysis was restricted to the summer season, NO_2 and CO, as well as PM_{10} and black smoke, showed significant univariate associations. In another, Schwartz (2001) later reported not only significant associations between PM_{10} exposures and plasma fibrinogen levels in a subset of the NHANES III cohort, but also PM_{10} associations with platelet and white cell counts, the PM_{10} associations being robust when O_3, NO_2, or SO_2 were included. CO was not analyzed.

The above findings add support for intriguing hypotheses about possible mechanisms by which PM exposure may be linked to adverse cardiac outcomes. They are interesting in implicating both increased blood viscosity and C-reactive protein, a biological marker of inflammatory responses thought to be predictive of increased risk for serious cardiac events.

8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies

Susceptible subpopulations. Because they lack extensive data on individual subject characteristics, hospital admissions studies provide only limited information on susceptibility factors based on stratified analyses. The relative effect sizes for PM-cardiovascular associations (and respiratory) admissions reported in ecologic time-series studies are generally somewhat higher than those for total admissions. This provides some limited support for hypothesizing that acute PM effects operate via cardiopulmonary pathways or that persons with pre-existing cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from ecologic time-series studies showing larger PM effects on cardiovascular admissions in adults aged ≥ 65 yr versus younger populations, the differences are neither striking nor consistent. One recent study reported larger CVD hospitalization among persons with current respiratory infections. The individual-level studies of cardiophysiologic function assessed above generally suggest that elderly persons with pre-existing cardiopulmonary disease are susceptible to subtle changes in heart rate variability in association with PM exposures. Because younger and healthier populations have not yet been much studied, it is not yet possible to say whether the elderly clearly have especially increased susceptibility.

Role of other environmental factors. The time-series studies published since 1996 have all controlled adequately for weather influences. Thus, it is deemed unlikely that residual confounding by weather accounts for the observed PM associations. With one possible exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac function. Thus, the possibility of confounding in such studies cannot yet be fully discounted. Co-pollutants have been analyzed extensively in many recent time-series studies of PM and hospital admissions. In some studies, PM clearly has an independent association after controlling for gaseous co-pollutants. In others, the PM effects are reduced once co-pollutants are added to the model; but this may be in part due to colinearity between PM_{10} and co-pollutants and/or gaseous pollutants (e.g., CO) having independent effects on cardiovascular function.

Temporal patterns of responses following PM exposure. The evidence from recent time-series studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at lag 0, with some carryover to lag 1, with little evidence for important effects beyond lag 1.

Relationship of CVD effects to PM size and chemical composition attributes. Insufficient data exist from the time-series CVD admissions studies or the emerging individual-level studies to provide clear guidance as to which ambient PM components, defined on the basis of size or composition, determine ambient PM CVD effect potency. The epidemiologic studies have been constrained by limited availability of multiple PM metrics. Where multiple metrics exist, they often are highly correlated or are of differential quality due to differences in numbers of monitoring sites and monitoring frequency.

PM effects on blood characteristics related to CVD events. Interesting, though limited, new evidence has also been derived which is highly suggestive of associations between ambient PM and increased blood viscosity, increased serum C-reactive protein, and fibrinogen (both related to increased risks of serious cardiac events). The biologic plausibility of these findings is supported by a study showing that ultrafine particles are rapidly distributed into the systemic circulation following inhalation exposure (Nemmar et al., 2002).

8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory-Related Hospital Admissions and Medical Visits

8.3.2.1 Introduction

Although hospital admissions represent one severe morbidity measure evaluated in regard to PM exposure, hospital emergency department (ED) visits are a notable related outcome. Doctors' visits also represent another related health measure that, although less studied, is still very relevant to assessing air pollution public health impacts. This category of pollution-affected persons can represent a large population, yet one largely unevaluated due to the usual lack of centralized data records for doctors' visits in the United States.

This section evaluates information on epidemiologic associations of ambient PM exposure with both respiratory hospital admissions and medical visits. It intercompares various studies examining size-related PM mass exposure measures (e.g., for PM_{10}, $PM_{2.5}$, etc.) or various PM chemical components vis-à-vis their associations with such health endpoints, and discusses their

respective extents of coherence with PM associations across related health effects measures. In the following discussion, the main focus for quantitative intercomparisons is on studies considering PM metrics that measure mass or a specific mass constituent, i.e., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, or sulfates (SO_4^{-2}). Study results for other related PM metrics (e.g., BS) are also considered, but only qualitatively, primarily with respect to their relative coherence with studies using mass or composition metrics measured in North America. In order to consider potentially confounding effects of other 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., O_3) is also included. Results from models with more than two pollutants included simultaneously, however, are not used for quantitative estimates of effect size or statistical strength, because of increased likelihood of bias and variance inflation due to multi-collinearity of various pollutants (e.g., see Harris, 1975).

8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document

In the 1996 PM AQCD, both COPD and pneumonia hospitalization studies were found to show moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 (or 6 to 25% excess risk increment) per 50 $\mu g/m^3$ PM_{10} increase or its equivalent. Whereas many hospitalizations for respiratory illnesses occur in those > 65 years of age, there were also increased hospitalizations for those < 65 years of age. Several hospitalization studies restricted their analysis by age group, but did not explicitly examine younger age groups. One exception noted was Pope (1991), who reported increased hospitalization for Utah Valley children (0 to 5 yrs) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies. Studies examining acute associations between indicators of components of fine particles (e.g., BS; sulfates, $SO_4^{=}$; and acidic aerosols, H^+) and hospital admissions were reported, too, as showing significant relationships. While sulfates were especially predictive of respiratory health effects, it was not clear whether the sulfate-related effects were attributable to their acidity, to the broader effects of associated combustion-related fine particles, or to other factors.

8.3.2.3 New Respiratory-Related Hospital Admissions Studies

New studies appearing since the 1996 PM AQCD have examined various admissions categories, including: total respiratory admissions for all ages and by age; asthma for all ages and by age; chronic obstructive pulmonary disease (COPD) admissions (usually for patients > 64 yrs.), and pneumonia admissions (for patients > 64 yrs.). Table 8B-2, Appendix 8B summarizes salient details regarding the study area, study period, study population, PM indices considered and their concentrations, methods employed, study results, and "bottom-line" PM index percent excess risks per standard PM increment (e.g., 50 $\mu g/m^3$ for PM_{10}) for the newer studies.

The percent excess risk (ER) estimates presented in Table 8B-2 are based upon the relative risks (RR's) provided by the authors, but converted into percent increments per standardized increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies (as discussed in Section 8.1). The ER's shown in the table are for the most positively significant pollutant coefficient; and the maximum lag model is used to provide estimates of potential pollutant-health effects associations.

Based on information from Dominici et al. (2002) indicating that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate (as discussed earlier), only those studies that used other statistical algorithms or which have reported reanalyzed S-Plus GAM results are assessed in the text below. However, given the modest effects of this reanalysis on most study results (i.e., while effect estimates are modified somewhat, the study conclusions remain largely unchanged), Table 8B-2 includes all studies and notes those that originally used the S-Plus GAM algorithm, as well as which of those studies have since been reanalyzed with more appropriate methods.

Of most pertinence here are those newly available studies that evaluate associations between one or another ambient PM metric and respiratory hospital admissions in U.S. or Canadian cities, as for PM_{10} mass concentrations are summarized in Table 8-17.

Among numerous new epidemiologic studies of PM_{10} morbidity, many evaluated relatively high PM_{10} levels. However, some did evaluate associations with PM_{10} concentrations ranging to rather low levels. Of note is the fact that associations have been reported by several investigators between acute PM_{10} exposures and total respiratory-related hospital admissions for numerous U.S. cities with annual mean PM_{10} concentrations extending to below 50 $\mu g/m^3$.

TABLE 8-17. SUMMARY OF UNITED STATES PM_{10} RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels (ug/m^3)	Co-Pollutants Measured	Day Lag	Method	Effect Estimate (95% CL) (% increase per 50 ug/m^3)
Schwartz et al. (1996b)	Respiratory	PM_{10} = 43	SO_3	—	Poisson GLM	5.8 (0.5, 11.4)
Samet et al. (2000a,b)*	COPD	PM_{10} = 33	SO_2, O_3, NO_2, CO	0 1	Default GAM Default GAM	7.4 (5.1, 9.8) 7.5 (5.3, 9.8)
Reanalysis by Zanobetti and Schwartz (2003b)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.4 (5.9, 12.9) 8.8 (4.8, 13.0) 6.8 (2.8, 10.8) 8.0 (4.3, 11.9)
Lippmann et al. (2000)*	COPD	PM_{10} = 31	SO_2, O_3, NO_2, CO, H^+	3 3	Default GAM Default GAM	No Co Poll: 9.6 (−5.3, 26.8) Co Poll: 1.0 (−15, 20)
Reanalysis by Ito (2003)				3	Default GAM Strict GAM NS GLM	No Co Poll: 9.6 (−5.3, 26.8) No Co Poll: 6.5 (−7.8, 23.0) No Co Poll: 4.6 (−9.4, 20.8)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	PM_{10} = 35, Chicago PM_{10} = 44, LA PM_{10} = 41, Phoenix PM_{10} = 44, LA	— — — CO	0 2 0 2	Default GAM: 30df Default GAM: 30df Default GAM: 30df Default GAM: 30df	2.4 (−0.2, 5.11) 6.1 (1.1, 11.3) 6.9 (−4.1, 19.3) 0.6 (−5.1, 6.7) (two poll. model)
Reanalysis by Moolgavkar (2003)	COPD (> 64 yrs)	Chicago		0	Strict GAM: 100df	3.24 (.031, 6.24)
Reanalysis by Moolgavkar (2003)	COPD (all ages)	Los Angeles		2 2 2	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	7.78 (4.32-10.51) 5.52 (2.53-8.59) 5.00 (1.22, 8.91)
Samet et al. (2000a,b)*	Pneumonia	PM_{10} = 33	SO_2, O_3, NO_2, CO	0 1	Default GAM Default GAM	8.1 (6.5, 9.7) 6.7 (5.3, 8.2)
Reanalysis by Zanobetti and Schwartz (2003b)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.9 (7.4, 12.4) 8.8 (5.9, 11.8) 2.9 (0.2, 5.6) 6.3 (2.5, 10.3)
Lippmann et al. (2000)	Pneumonia	PM_{10} = 31	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co Poll: 21.4 (8.2, 36.3) Co Poll: 24 (8.2, 43)
Reanalysis by Ito (2003)	Pneumonia			1 1 1	Default GAM Strict GAM NS GLM	No Co Poll: 21.5 (8.3, 36) No Co-Poll: 18.1 (5.3, 32.5) No Co-Poll: 18.6 (5.6, 33.1
Jacobs et al. (1997)	Asthma	PM_{10} = 34	O_3, CO	—	Poisson GLM	6.11 (CI not reported)
Nauenberg and Basu (1999)	Asthma	PM_{10} = 45	O_3	0	Poisson GLM	16.2 (2.0, 30)
Tolbert et al. (2000b)	Asthma	PM_{10} = 39	O_3, NO_X	1	GEE	13.2 (1.2, 26.7)
Sheppard et al. (1999)*	Asthma	PM_{10} = 31	CO, O_3, SO_2	1	Default GAM	13.2 (5.5, 22.6)
Reanalysis by Sheppard (2003)					NS GLM Strict GAM	10.9 (2.8, 19.6) 8.1 (0.1, 16.7)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model

On this account, the results of the NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} levels and hospital admissions by persons ≥ 65 in 14 U.S. cities are of particular interest. As noted in Table 8-18, this study indicates PM_{10} effects similar to other cities, but with narrower confidence bands, due to its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each had mean PM_{10} below 50 $\mu g/m^3$. The cities considered and their respective annual mean/daily maximum PM_{10} concentrations (in $\mu g/m^3$) are Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago (36.4/144.7); Colorado Springs (26.9/147.2); Detroit (36.8/133.6); Minneapolis/St Paul (36.8/133.6); Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3); Provo/Orem (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown (33.1/104.0).

Table 8-18 also shows results of reanalyzing a number of the models considered in original research with the use of models using more stringent convergence requirements than the original default option. These results show that the effect estimates decline somewhat, but that the basic direction of effect and conclusions about the significance of the PM effect on hospital admissions remained unchanged.

Zanobetti and Schwartz (2003b), in their reanalyses, also considered spline models that are thought to better estimate confidence intervals around pollutant effect estimates than the original GAM analyses. With the spline models, confidence intervals usually increased over the original GAM model and the coefficients also decreased somewhat (similar to GAM with more stringent convergence criteria). As for possible co-pollutant confounding, it was reported that "In our previous studies we did not find confounding due to other pollutants. These results are confirmed in this reanalysis by the meta-regression analyses." Overall, the authors concluded that "the general result is that the association of PM_{10} with hospital admissions remains and in most cases is little changed."

Janssen et al. (2002) did further analyses for the Samet et al. (2000a,b) 14-city data set examining associations for variable prevalence in air-conditioning (AC) and/or contributions of different sources to total PM_{10}. For COPD and pneumonia, the associations were less significant, but the pattern of association was similar to that for CVD. The Zanobetti and

TABLE 8-18. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-μg/m^3 INCREASE IN PM_{10} IN 14 U.S. CITIES (ORIGINAL AND REANALYZED RESULTS)

Constrained lag models (Fixed Effect Estimates)	% Increase	CVD (95% CI)	% Increase	COPD (95% CI)	% Increase	Pneumonia (95% CI)
Original One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Original Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Original Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
Reanalyzed Two day mean (for lag 0 and 1)	0.99	(0.79, 1.19)	1.71	(0.95, 2.48)	1.98	(1.65, 2.31)
Original $PM_{10} < 50$ μg/m^3 (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Reanalyzed $PM_{10} < 50$ μg/m^3 (two day mean)	1.32	(0.77, 1.87)	2.21	(1.02, 3.41)	1.06	(0.06, 2.07)
Original Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Reanalyzed Quadratic distributed lag	1.09	(0.81, 1.38)	2.53	(1.20, 3.88)	1.47	(0.86, 2.09)
Unconstrained distributed lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.90	(1.46, 2.34)
Original Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)
Reanalyzed Random effects estimate	1.12	(0.84, 1.40)	2.53	(1.21, 3.87)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b) and Zanobetti and Schwartz (2003b) reanalyses.

Schwartz (2003b) reanalyses also examined these results, and they stated that "We still found a decreased PM_{10} effect with increasing percentage of home with central AC."

Moolgavkar (2003) also reanalyzed his earlier GAM analyses of hospital admissions for chronic obstructive pulmonary disease (Moolgavkar, 2000c) Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models; but the magnitudes of the risk estimates dropped by more than half to non-statistically significant levels in two-pollutant models including CO. However, unlike the meta-regression approach to the multiple pollutant

issue used by Zanobetti and Schwartz (2003b), simultaneous regression of moderately to highly correlated pollutants can lead to biased pollutant coefficients and commonly results in diminished effect estimates for some or all of the pollutants considered. In the same study, similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0-19 yr; 20-64 yr) in Los Angeles, as well.

In his reanalyses of these GAM results using the more stringent convergence criteria, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect of using the more stringent convergence criteria on the results. In the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing more stringent convergence criteria; so direct before/after comparisons are not possible for Moolgavkar's (2003) Chicago analyses. Moolgavkar noted that "changes in the convergence criteria and the use of GLM instead of GAM can, but does not always, have substantial impact on the results of the analyses and their interpretation." He also concluded: "Given that different analytic strategies can make substantial differences to the estimates of effects of individual pollutants I do not believe that these numerical estimates are too meaningful. Patterns of association appear to be robust, however. For example, in Los Angeles, with the exception of COPD admissions with which NO_2 appears to show the most robust association, it is clear that CO is the best single index of air pollution associations with health end points, far better than the mass concentration of either PM_{10} or of $PM_{2.5}$. In Cook County the results are not so clear-cut, however, any one of the gases is at least as good an index of air pollution effects on human health as is PM_{10}."

Tolbert et al. (2000b) used generalized estimating equations (GEE), logistic regression, and Baysian models to evaluate associations between emergency department visits for asthma (by those < 17 yrs old) in Atlanta during the summers of 1993 – 1995 (~ 6000 visits for asthma out of ~ 130,000 total visits) and several air pollution variables (PM_{10}, O_3, total oxides of nitrogen). Logistic regression models controlling for temporal and demographic variables gave statistically significant ($p < 0.05$) lag 1 day relative risk estimates of 1.04 per 15 $\mu g/m^3$ 24-h PM_{10} increment and 1.04 per 20 ppb increase in maximum 8-h O_3 levels. In multipollutant models including both PM_{10} and O_3, the terms for each became non-significant due to high collinearity of the two

variables ($r^2 = 0.75$). The authors interpreted their findings as suggesting positive associations between pediatric asthma visits and both PM_{10} and O_3. The PM_{10} effects appeared to be stronger for concentrations > 20 $\mu g/m^3$ than below that 24-h value.

Other U.S. studies finding associations of respiratory-related hospital admissions or medical visits with PM_{10} levels extending below 50 $\mu g/m^3$ include: Schwartz (1994) in Minneapolis-St. Paul, Minnesota; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999) in Seattle; Linn et al. (2000) in Los Angeles; and Nauenberg and Basu (1999) in Los Angeles; in Minneapolis-St. Paul, MN, but not in Birmingham, AL. The excess risk estimates most consistently fall in the range of 5 to 25% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma visits and hospital admissions often being higher than those for COPD and pneumonia admissions.

Similar associations between increased respiratory related hospital admissions/medical visits and low short-term PM_{10} levels were also reported by various investigators for several non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant associations between PM_{10} (mean = 25.6 $\mu g/m^3$, max. = 131 $\mu g/m^3$) and respiratory admissions in Birmingham, UK using multivariate linear regression methods; and Atkinson et al. (1999b), using Poisson modeling, reported significant increases in hospital admissions for respiratory disease to be associated with PM_{10} (mean = 28.5 $\mu g/m^3$) in London, UK. Hagen et al. (2000) and Prescott et al. (1998) also found positive but non-significant associations of hospital admissions and, PM_{10} levels in Drammen, Norway (mean = 16.8 $\mu g/m^3$) and Edinburgh, Scotland (mean = 20.7 $\mu g/m^3$). Admissions in Drammen considered relatively small populations, limiting statistical power in this study. Petroeschevsky et al. (2001) examined associations between outdoor air pollution and hospital admissions in Brisbane, Australia during 1987-1994 using a light scattering index (BSP) for fine PM. The levels of PM are quite low in this city, relative to most U.S. cities, but BSP was positively and significantly associated with total respiratory admissions, but not for asthma.

If day-to-day increases in air pollution cause increases in hospital admissions, as shown by time-series studies, then short-term removal of pollution should lower admissions. It is rarely possible to test this hypothesis by examining a situation when pollution sources are abruptly "turned off" and then "turned on" again. One such opportunity did arise when a steel mill strike resulted in concomitant reductions in both PM and respiratory admissions that were experienced

in Utah Valley, but not in surrounding valleys without the steel mill, as documented by Pope (1991). A perhaps more broadly relevant case where this hypothesis was similarly tested was a study of air quality improvements during the Atlanta Summer Olympics of 1996 (Friedman et al., 2001). Potential associations between air quality improvements and changes in children's hospital admissions, while weather and other "natural" influences on admissions remained unchanged from normal, were evaluated by Friedman et al. Interestingly, compared to a baseline period, traffic related pollution declined, as did PM_{10} levels by 16% and O_3 by 28% as a result of the alternative mass transportation strategy used to reduce road traffic during the Games. At the same time, SO_2, not related to traffic, actually increased during the Games. Both PM and O_3 concentrations also rose noticeably after the Olympics. A significant reduction in asthma events was associated with O_3 concentrations, but the PM_{10} association was not statistically significant. While the high correlation between PM and O_3 limit the ability to determine which pollutant may account for the reduction in asthma events, this study supports the hypothesis that reductions of acute air pollution can provide immediate health improvements.

8.3.2.3.1 Particulate Matter Mass Fractions and Composition Comparisons

While PM_{10} mass has generally been the metric most often used as the particle pollution index in the U.S. and Canada, some new studies have examined the relative roles of various PM_{10} mass fractions (e.g., $PM_{2.5}$ and $PM_{10-2.5}$) and chemical constituents (such as SO_4^{-2}) contributing to PM-respiratory hospital admissions associations. Several new studies (from among those summarized in Tables 8-19 and 8-20, respectively) report significant associations of increased respiratory-cause medical visits and/or hospital admissions with ambient $PM_{2.5}$ and/or $PM_{10-2.5}$ ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit, where all PM metrics (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, H^+) were positively related to pneumonia and COPD admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values for pneumonia generally remaining little changed (but with broader confidence intervals) in multipollutant models including one or more gaseous pollutant (e.g., CO, O_3, NO_2, SO_2). However, for COPD admissions, the effect estimates were reduced and became non-significant in multipollutant models including gaseous copollutants. Excess risks for pneumonia admissions in the one pollutant model using default GAM were 13% (3.7, 22)

TABLE 8-19. SUMMARY OF UNITED STATES $PM_{2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m^3	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL) (% increase per 25 ug/m^3)
Lippmann et al. (2000)	COPD	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H+	3 3	Default GAM Default GAM	No Co Poll: 5.5 (–4.7, 16.8) Co Poll: 2.8 (–9.2, 16)
Reanalysis by Ito (2003)	COPD				Default GAM Strict GAM NS GLM	No Co Poll: 5.5 (–4.7, 16.8) No Co Poll: 3.0(–6.9, 13.9) No Co Poll: 0.3(–9.3, 10.9)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	$PM_{2.5}$ = 22, LA $PM_{2.5}$ = 22, LA	— CO	2 2	Default GAM Default GAM	5.1 (0.9, 9.4) 2.0 (-2.9, 7.1) Two poll. model
Reanalysis by Moolgavkar (2003)	COPD (all ages)			2 2 2	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	4.69 (2.06, 7.38) 2.87 (0.53, 5.27) 2.59 (-0.29, 5.56)
Lippmann et al. (2000)	Pneumonia	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co-Poll: 12.5 (3.7, 22.1) Co Poll: 12 (1.7, 23)
Reanalysis by Ito (2003)	Pneumonia				Default GAM Strict GAM NS GLM	No Co-Poll: 12.5 (3.7, 22.1) No Co-Poll: 10.5 (1.8, 19.8) No Co-Poll: 10.1 (1.5, 19.5)
Sheppard et al. (1999)*	Asthma	$PM_{2.5}$ = 16.7	CO, O_3, SO_2	1	Default GAM	8.7 (3.3, 14.3)
Reanalysis by Sheppard (2003)			CO		Default GAM Strict GAM NS GLM Strict GAM NS GLM	No Co-Poll: 8.7 (3.3, 14.3) No Co-Poll: 8.7 (3.2,14.4) No Co-Poll: 6.5 (1.1,12.0) With Co-poll: 6.5 (2.1, 10.9) With Co-poll: 6.5 (2.1, 10.9)
Freidman et al. (2001)	Asthma	$PM_{2.5}$ = (36.7-30.8 decrease)	O_3	3 d. cum	Poisson GEE	1.4 (0.80-2.48)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

and 12% (–0.6, 24) per 25 μg/m^3 of $PM_{2.5}$ and $PM_{10-2.5}$, respectively; those for COPD admissions were 5.5% (–4.7, 17) and 9.3% (–4.2, 25) per 25 μg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$, respectively.

Lippmann et al. (2000) reported weaker associations with sulfate and acidic components of $PM_{2.5}$ than with $PM_{2.5}$ mass overall, but the acidity levels during this study were very low, being below detection on most study days. In contrast, past studies of sulfates and aerosol acidity associations with respiratory hospital admissions have found stronger sulfate associations when the acidity of those aerosols was higher (e.g., Thurston et al, 1994). As noted by Lippman et al.

TABLE 8-20. SUMMARY OF UNITED STATES $PM_{10-2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m^3	Co-Pollutants Measured	Lag	Method	Effect Estimates (95% CL) (% increase per 25 ug/m^3)
Moolgavkar (2000c)*	COPD		—	3	Default GAM	5.1% (−0.4, 10.9)
Lippmann et al. (2000)*	COPD	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H+	3 3	Default GAM Default GAM	No Co-Poll: 9.3 (−4.2, 24.7) Co-Poll: 0.3 (−14, 18)
Reanalysis by Ito (2003)					Default GAM Strict GAM NS GLM	No Co-Poll: 9.3 (−4.2, 24.7) No Co-Poll: 8.7 (−4.8, 24.0) No Co-Poll: 10.8 (−3.1, 26.5)
Lippmann et al. (2000)*	Pneumonia	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co-Poll: 11.9 (−0.6, 24.4) Co-Poll: 13.9 (0.0, 29.6)
Reanalysis by Ito (2003)				1 1 1	Default GAM Strict GAM NS GLM	No Co-Poll: 11.9 (−0.6, 24.4) No Co-Poll: 9.9 (−0.1, 22.0) No Co-Poll: 11.2 (−0.02, 23.6)
Sheppard et al. (1999)*	Asthma	$PM_{10-2.5}$ = 16.2	CO, O_3, SO_2	1	Default GAM	11.1 (2.8, 20.1)
Reanalysis by Sheppard (2003)				1 1	Strict GAM NS GLM	5.5 (−2.7 11.1) 5.5 (0, 14.0)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

(2000), "a notable difference between the data of Thurston and colleagues from Toronto and our data is the H^+ levels: the H^+ levels in Toronto were 21.4, 12.6, and 52.3 nmol/m^3 for the summers of 1986, 1987, and 1988, respectively, whereas in our study, the H^+ level averaged only 8.8 nmol/m^3." Thus, these results are consistent with past studies and biological plausibility, in that sulfates and its associated PM should be less toxic when in a less strongly acidic form, as indeed found in this study.

In order to evaluate the potential influence of the Generalized Additive Model (GAM) convergence specification on the results of the original Detroit data analysis, Ito (2003) re-examined associations between PM components and daily mortality/morbidity by using more stringent GAM convergence criteria, and by applying a Generalized Linear Models (GLM) that approximated the original GAM models. The reanalysis of GAM Poisson models used more stringent convergence criteria, as suggested by Dominici et al. (2002): the convergence precision (epsilon) was set to 10-14 and maximum iteration was set to 1000, for both the local scoring and

back-fitting algorithms. The GLM model specification approximated the original GAM models. Natural splines were used for smoothing terms. To model time trend, the same degrees of freedom as the smoothing splines in the GAM models were used, with the default placement of knots. For weather models, to approximate LOESS smoothing with a span of 0.5 in the GAM model, natural splines with degrees of freedom were used. Generally, the GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller estimated relative risks than those reported in the original study, e.g., for respiratory admissions in Table 8-21. It was found that the reductions in the estimated relative risks were not differential across the PM indices. Thus, conclusions of the original study about the relative roles of PM components by size and chemical characteristics remained unaffected.

TABLE 8-21. INTERCOMPARISON OF DETROIT PNEUMONIA HOSPITAL ADMISSION RELATIVE RISKS (± 95% CI below) OF PM INDICES (per 5th-to-95th percentile pollutant increment) FOR VARIOUS MODEL SPECIFICATIONS.*

	Original GAM (default)	GAM (stringent)	GLM
$PM_{2.5}$ (1)	1.185 (1.053, 1.332)	1.154 (1.027, 1.298)	1.149 (1.022, 1.292)
$PM_{10-2.5}$ (1)	1.114 (1.006, 1.233)	1.095 (0.990, 1.211)	1.107 (1.00, 1.226)
PM_{10} (1)	1.219 (1.084, 1.372)	1.185 (1.054, 1.332)	1.190 (1.057, 1.338)
H^+ (3)	1.060 (1.005, 1.118)	1.049 (0.994, 1.107)	1.049 (0.994, 1.107)
$SO_4^=$ (1)	1.156 (1.050, 1.273)	1.128 (1.025, 1.242)	1.123 (1.020, 1.235)

*The selected lag is indicated in parenthesis next to the pollutant name.

Source: Ito (2003).

Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data from hospital admissions for respiratory disease on King County, WA for eight years (1987-94), together with air pollution and weather information, using estimating equations and weighted empirical variance estimators. However, their weather controls were relatively crude (i.e.,

seasonal dummy variables and linear temperature terms). This study is notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$ and for finding significant hospital admission associations only with $PM_{1.0}$. This may suggest that the $PM_{2.5}$ versus PM_{10} separation may not always be sufficient to differentiate submicron fine particle versus coarse-particle toxicities.

Asthma hospital admission studies in various U.S. communities provide additional important new data. Of particular note is a study by Sheppard et al. (1999) which evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3, and CO) and non-elderly adult (< 65 years of age) hospital admissions for asthma in Seattle, WA. PM and CO were found to be jointly associated with asthma admissions. An estimated 4 to 5% increase in the rate of asthma hospital admissions (lagged 1 day) was reported to be associated with interquartile range changes in PM indices (19 $\mu g/m^3$ for PM_{10}, 11.8 $\mu g/m^3$ for $PM_{2.5}$, and 9.3 $\mu g/m^3$ for $PM_{10-2.5}$), equivalent to excess risk rates as follows: 13% (CI = 05-23) per 50 $\mu g/m^3$ for PM_{10}; 9% (CI = 3-14) per 25 $\mu g/m^3$ $PM_{2.5}$; 11% (CI = 3-20) per 25 $\mu g/m^3$ $PM_{10-2.5}$. Also of note for the same region by the same research team using similar methods is the Norris et al. (1999) study showing associations of low levels of $PM_{2.5}$ (mean = 12 $\mu g/m^3$) with markedly increased asthma ED, i.e., excess risk = 44.5% (CI = 21.7-71.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

Sheppard (2003) recently conducted a reanalysis of their nonelderly hospital admissions data for asthma in Seattle, WA, to evaluate the effect of the fitting procedure on their previously published analyses. As shown in Figure 8-13, the effect estimates were slightly smaller when more stringent convergence criteria were used with GAM, and there was an additional small reduction in the estimates when GLM with natural splines were used instead. Confidence intervals were slightly wider for the GLM model fit. Sheppard concluded that, "Overall the results did not change meaningfully. There were small reductions in estimates using the alternate fitting procedures. I also found that the effect of single imputation (i.e., not adjusting for replacing missing exposure data with an estimate of its expected value) was to bias the effect estimates slightly upward. In this data set this bias is of the same order as the bias from using too liberal convergence criteria in the generalized additive model."

Moolgavkar (2003) also conducted reanalyses of respiratory-related hospital admissions, but for COPD data for all ages in Los Angeles. Using GAM with strict convergence criteria and 30 degrees of freedom (df), an excess risk estimate of 4.7% (CI = 2.1 – 7.4) was obtained per

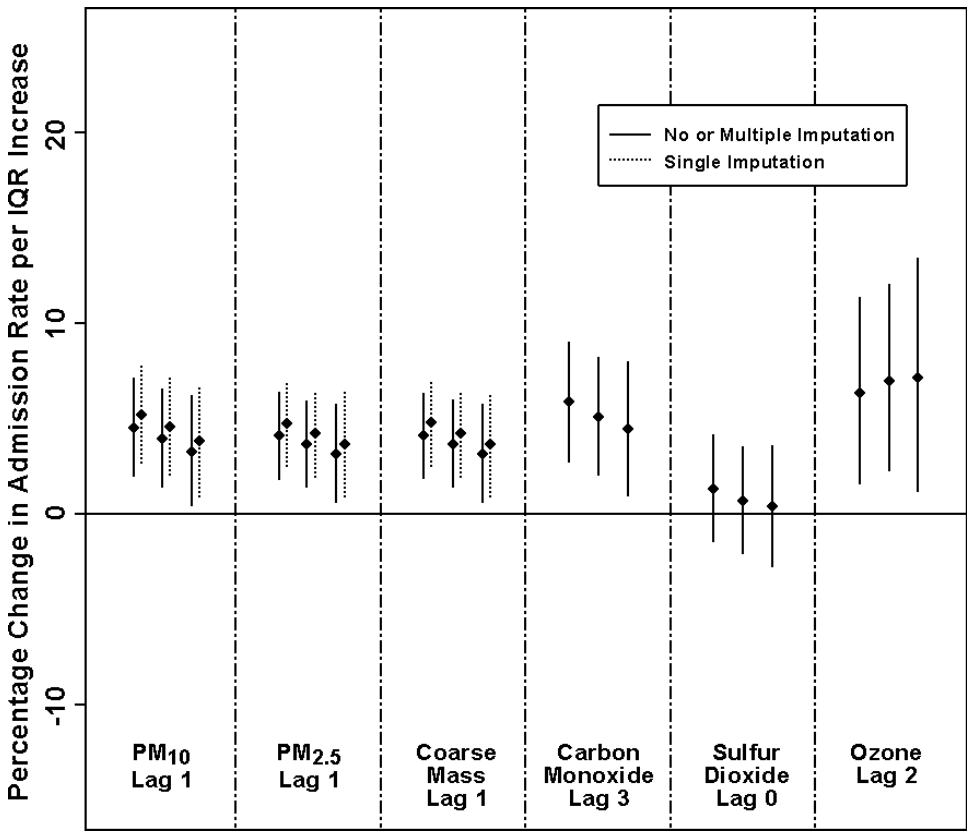

Figure 8-13. Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma. Poisson regression models are adjusted for time trends (64-df spline), day-of-week, and temperature (4-df spline). The IQR for each pollutant equals: 19 ug/m^3 for PM_{10}, 11.8 ug/m^3 for $PM_{2.5}$, 9.3 ug/m^3 for coarse PM, 20 ppb for O_3, 4.9 ppb for SO_2, and 924 ppb for CO. Triplets of estimates for each pollutant are for the original GAM analysis using smoothing splines, the revised GAM analysis with stricter convergence criteria, and the GLM analysis with natural splines. For pollutants that required imputation (i.e., estimation of missing value) estimates ignoring (single imputation) or adjusting for (multiple imputation) the imputation are shown.

Source: Sheppard (2003).

25 µg/m^3 $PM_{2.5}$ increment. The notable effect of increasing degrees of freedom on modeling results is well illustrated by the excess risk estimate dropping to 2.9% (CI = 0.5 – 5.3) with strict GAM and 100 df or 2.6% (CI = –0.3, 5.6) with NS GLM 100 df.

Burnett et al. (1997a) evaluated the role that the ambient air pollution mix, comprised of gaseous pollutants and PM indexed by various physical and chemical measures, plays in exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases (tracheobronchitis, chronic obstructive lung disease, asthma, and pneumonia). They employed daily measures of $PM_{2.5}$ and $PM_{10-2.5}$, aerosol chemistry (sulfates and H+), and gaseous pollutants (O_3, NO_2, SO_2, CO) collected in Toronto, Ontario, Canada, during the summers of 1992, 1993, and 1994. Positive associations were observed for all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most consistently significant pollutant and least sensitive to adjustment for other gaseous and particulate measures. The PM associations with respiratory hospital admissions were significant for: PM_{10} (RR = 1.11 for 50 μg/m^3; CI = 1.05-1.17); $PM_{2.5}$ (fine) mass (RR = 1.09 for 25 μg/m^3; CI = 1.03-1.14);$PM_{10-2.5}$ (coarse) mass (RR = 1.13 for 25 μg/m^3; CI = 1.05-1.20); sulfate levels (RR = 1.11 for 155 nmoles/m^3 = 15 μg/m^3; CI = 1.06-1.17); and H^+ (RR = 1.40 for 75 nmoles/m^3 = 3.6 μg/m^3, as H_2SO_4; CI = 1.15-1.70). After inclusion of O_3 in the model, the associations with the respiratory hospital admissions remained significant for: PM_{10} (RR = 1.10, CI = 1.04-1.16); fine mass (RR = 1.06; CI = 1.01-1.12); coarse mass (RR = 1.11; CI = 1.04-1.19); sulfate levels (RR = 1.06; CI = 1.0-1.12); and H^+ (RR = 1.25; CI = 1.03-1.53), using the same increments. Of the PM metrics considered here, H^+ yielded the highest RR estimate. Regression models that included all recorded pollutant simultaneously (with high intercorrelations among the pollutants) were also presented.

There have also been numerous new time-series studies examining associations between air pollution and respiratory-related hospital admissions in Europe, as summarized in Appendix 8B, Table 8B-2, but most of these studies relied primarily on black smoke (BS) as their PM metric. BS is a particle reflectance measure that provides an indicator of PM blackness and is highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton, 1982). In the U.S., Coefficient of Haze (CoH) is a metric of particle transmittance that similarly most directly represents a metric of particle blackness and ambient elemental carbon levels (Wolff et al., 1983) and has been found to be highly correlated with BS (r = 0.9; Lee et al., 1972). However, the relationship between airborne carbon and total mass of overall aerosol (PM) composition varies over time and from locality to locality, so the BS-mass ratio is less reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-mass relationship is likely to be very different between Europe and the U.S., largely due to differences

in local PM source characteristics (e.g., percentages of diesel powered motor vehicles). Therefore, while these European BS-health effects studies may be of qualitative interest for evaluating the PM-health effects associations, they are not as useful for quantitative assessment of PM effects relevant to the U.S.

Probably the most extensive and useful recent European air pollution health effects analyses have been conducted as part of the APHEA multi-city study, which evaluated 15 European cities from 10 different countries with a total population of over 25 million. All studies used a standardized data collection and analysis approach, which included consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2, and O_3) and the use of time-series regression addressing seasonal and other long-term patterns; influenza epidemics; day of the week; holidays; weather; and autocorrelation (Katsouyanni et al., 1996). The general coherence of the APHEA results with other results gained under different conditions strengthens the argument for causality in the air pollution-health effects association. In earlier studies, the general use of the less comparable suspended particle (SPM) measures and BS as PM indicators in some of the APHEA locations and analyses lessens the quantitative usefulness of such analyses in evaluating associations between PM and health effects most pertinent to the U.S. situation. However, Atkinson et al. (2001) report results of PM_{10} analyses in a study of eight APHEA cities.

As for other single-city European studies of potential interest here, Hagan et al. (2000) compared the association of PM_{10} and co-pollutants with hospital admissions for respiratory causes in Drammen, Norway during 1994-1997. Respiratory admissions averaged only 2.2 per day; so, the power of this analysis is weaker than studies looking at larger populations and longer time periods. The HEI I.B Multi-city Report modeling approach was employed. While a significant association was found for PM_{10} as a single pollutant, it became non-significant in multiple pollutant models. In two pollutant models, the associations and effect size of pollutants were generally diminished, and when all eight pollutants were considered in the model, all pollutants became non-significant. These results are typical of the problems of analyzing and interpreting the coefficients of multiple pollutant models when the pollutants are even moderately inter-correlated over time. A unique aspect of this work was that benzene was considered in this community strongly affected by traffic pollution. In two pollutant models, benzene was most consistently still associated. The authors conclude that PM is mainly an

indicator of air pollution in this city and emissions from vehicles seem most important for health effects. Thompson et al. (2001) report a similar result in Belfast, Northern Ireland, where, after adjusting for multiple pollutants, only the benzene level was independently associated with asthma emergency department (ED) admissions.

8.3.2.4 Key New Respiratory Medical Visits Studies

As discussed above, medical visits include both hospital ED visits and doctors' office visits. As in the past PM AQCD's, most available morbidity studies in Table 8B-3, Appendix 8B and in Table 8-22 below are of ED visits and their associations with air pollution. These studies collectively confirm the results provided in the previous AQCD, indicating a positive and generally statistically significant association between ambient PM levels and increased respiratory-related hospital visits.

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 ($\mu g/m^3$)	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL)
PM_{10}						
Choudhury et al. (1997)	Asthma	41.5	Not considered	0	GLM	20.9 (11.8, 30.8)
Lipsett et al. (1997)	Asthma	61.2	NO_2, O_3	2	GLM	34.7 (16, 56.5) at 20 °C
Tolbert et al. (2000b)	Asthma	38.9	O_3	1	GEE	SP 13.2 (1.2, 26.7)
Tolbert et al. (2000a)*	Asthma	29.1	NO_2, O_3, CO, SO_2	0-2	GLM	SP 8.8 (−8.7, 54.4)
$PM_{2.5}$						
Tolbert et al. (2000a)*	Asthma	19.4	NO_2, O_3, CO, SO_2	0-2	GLM	SP 2.3 (−14.8, 22.7)
$PM_{10-2.5}$						
Tolbert et al. (2000a)*	Asthma	9.39	NO_2, O_3, CO, SO_2	0-2	GLM	SP 21.1 (−18.2, 79.3)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model; SP = Single Pollutant Model; MP = Multipollutant Model

*Preliminary results based on emergency department visit data from 18 of 33 participating hospitals.

Of the medical visit and hospital admissions studies since the 1996 PM AQCD, among the most informative are those that evaluate health effects at levels below previously well-implicated PM concentrations. As for U.S. studies, Tolbert et al. (2000b) reported a significant PM_{10} association with pediatric ED visits in Atlanta where mean PM_{10} = 39 $\mu g/m^3$ and maximum PM_{10} = 105 $\mu g/m^3$. The Lipsett et al. (1997) study of winter air pollution and asthma emergency visits in Santa Clara Co, CA, may provide insight where one of the principal sources of PM_{10} is residential wood combustion (RWC). Their results demonstrate an association between PM levels and asthma. Also of interest, Delfino et al. (1997) found significant PM_{10} and $PM_{2.5}$ associations for respiratory ED visits among older adults in Montreal when mean PM_{10} = 21.7 $\mu g/m^3$ and mean $PM_{2.5}$ = 12.2 $\mu g/m^3$. Hajat et al. (1999) also reported significant PM_{10} associations with asthma doctor's visits for children and young adults in London when mean PM_{10} = 28.2 $\mu g/m^3$ and the PM_{10} 90^{th} percentile was only 46.4 $\mu g/m^3$. Overall, then, several new medical visits studies indicate PM-health effects associations at lower $PM_{2.5}$ and PM_{10} levels than demonstrated previously for this health outcome.

8.3.2.4.1 Scope of Medical Visit Morbidity Effects

Several newer medical visit studies consider a new endpoint for comparison with ED visits: visits in the primary care setting. In particular, key studies showing PM associations for this health outcome include: the study by Hajat et al. (1999) that evaluated the relationship between air pollution in London, UK; and daily General Practice (GP) doctor consultations for asthma and other lower respiratory disease (LRD); the study by Choudhury et al. (1997) of private asthma medical visits in Anchorage, Alaska; and the study by Ostro et al. (1999b) of daily visits by young children to primary care health clinics in Santiago, Chile for upper or lower respiratory symptoms.

While limited in number, the above studies collectively provide new insight into the fact that there is a broader scope of severe morbidity associated with PM air pollution exposure than previously documented. As the authors of the London study note: "There is less information about the effects of air pollution in general practice consultations but, if they do exist, the public health impact could be considerable because of their large numbers." Indeed, the London study of doctors' GP office visits indicates that the effects of air pollution, including PM, can affect many more people than indicated by hospital admissions alone.

These new studies also provide indications as to the quantitative nature of medical visits effects, relative to those for hospital admissions. In the London case, comparing the number of admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study (Hajat et al., 1999) indicates that there are circa 24 asthma GP visits for every asthma hospital admission in that city. Also, comparing the PM_{10} coefficients indicates that the all-ages asthma effect size for the GP visits (although not statistically different) was about 30% larger than that for hospital admissions. Thus, these new studies suggest that looking at only hospital admissions and emergency hospital visit effects may greatly underestimate the overall numbers of respiratory morbidity events due to acute ambient PM exposure.

8.3.2.4.2 Factors Potentially Affecting Respiratory Medical Visit Study Outcomes

Some newly available studies have examined certain factors that might extraneously affect the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias and random variability in diagnostic classification of air pollution and daily cardiac or respiratory ED visits, such as for asthma, COPD, respiratory infection, etc. They concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels. Also, Stieb et al. (1998b) reported that for a population of adults visiting an emergency department with cardiac respiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability in average personal exposure to particulate sulfate, whereas acid exposure was not as well represented by fixed site monitors. Another study investigated possible confounding of respiratory visit effects due to pollens (Steib et al, 2000). Pollen levels did not influence the results, similar to asthma panel studies described below in Section 8.3.3. In London, Atkinson et al. (1999b) studied the association between the number of daily ED visits to for respiratory complaints and measures of outdoor air pollution for PM_{10}, NO_2, SO_2 and CO. They examined different age groups and reported strongest associations for children for visits for asthma, but were unable to separate PM_{10} and SO_2 effects.

8.3.2.5 Identification of Potential Susceptible Subpopulations

Associations between ambient PM measures and respiratory admissions have been found for all age groups, but older adults and children generally have been indicated by hospital admissions studies to exhibit the most consistent PM-health effects associations. As reported in

previous PM AQCDs, numerous studies of older adults (e.g., those 65+ years of age) have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Anderson et al, 1998). However, only a limited number have specifically studied children as a subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital admissions associations as a function of age in Ontario, reporting that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age).

Further efforts have aimed at identifying and quantifying air pollution effects among potentially especially susceptible sub-populations of the general public. Some new studies have further investigated the hypothesis that the elderly are especially affected by air pollution. Zanobetti et al. (2000a) examined PM_{10} associations with hospital admissions for heart and lung disease in ten U.S. cities, finding an overall association for COPD, pneumonia, and CVD. They found that these results were not significantly modified by poverty rate or minority status in this population of Medicare patients. Ye et al. (2001) examined emergency transports to the hospital. Both PM_{10} and $N0_2$ levels were significantly associated with daily hospital transports for angina, cardiac insufficiency, myocardial infarction, acute and chronic bronchitis, and pneumonia. The pollutant effect sizes were generally found to be greater in men than in women, except those for angina and acute bronchitis, which were the same across genders. Thus, in these various studies, cardiopulmonary hospital visits and admissions among the elderly were seen to be consistently associated with PM levels across numerous locales in the U.S. and abroad, generally without regard to race or income; but sex was sometimes an effect modifier.

Several new studies of children's morbidity also support the indication of air pollution effects among children. Pless-Mulloli et al. (2000) evaluated children's respiratory health and air pollution near opencast coal mining sites in a cohort of nearly 5,000 children aged 1-11 in England. Mean PM levels were not high (mean < 20 $\mu g/m^3$ PM_{10}), but statistically significant PM_{10} associations were found with respiratory symptoms. A roughly 5 percent increase of General Practitioner medical visits was also noted, but was not significant. Ilabaca et al. (1999) also found an association between levels of fine PM and ED visits for pneumonia and other respiratory illnesses among children < 15 years in Santiago, Chile, where the levels of $PM_{2.5}$ were very high (mean = 71.3 $\mu g/m^3$) during 1995-1996. The authors found it difficult to separate out the effects of various pollutants, but concluded that PM (especially the fine component) is associated with the risk of these respiratory illnesses. Overall, these new studies support past

assertions that children, and especially neo-natal infants, are especially susceptible to the health effects of air pollution.

The respiratory-related hospital admissions studies summarized in Appendix 8B reveal that the PM RR's for all children (e.g., 0-18) are not often notably larger than those for adults, but such comparisons of RR's must adjust for differences in baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per $\mu g/m^3$ that is half that of the adults given the exact same impact on admissions/100,000/$\mu g/m^3$/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially regarding the population catchment for each age group in each study). One of the few indications that is notable when comparing children with other age group effect estimates in Table 8B-2 is the higher excess risk estimate for infants (i.e., the group < 1 yr. of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate roughly twice as large as for other children or adults.

8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits

The results of new studies discussed above are generally consistent with and supportive of findings presented in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a), with regard to ambient PM associations of short-term exposures with respiratory-related hospital admissions/medical visits. Figure 8-14 summarizes results for maximum excess risk of respiratory-related hospital admission and visits per 50 $\mu g/m^3$ PM_{10} based on single-pollutant models for selected U.S. cities. The excess risk estimates fall most consistently in the range of 5 to 20% per 50 $\mu g/m^3$ PM_{10} increments, with those for asthma visits and hospital admissions generally somewhat higher than for COPD and pneumonia hospital admissions. More limited new evidence both (a) substantiates increased risk of respiratory-related hospital admissions due to ambient fine particles ($PM_{2.5}$, $PM_{1.0}$, etc.) and also (b) points towards such admissions being associated with ambient coarse particles ($PM_{10-2.5}$). Excess risk estimates tend to fall in the range of ca. 5.0 to 15.0% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ for overall respiratory admissions or for COPD admissions, whereas larger estimates are found for asthma admissions.

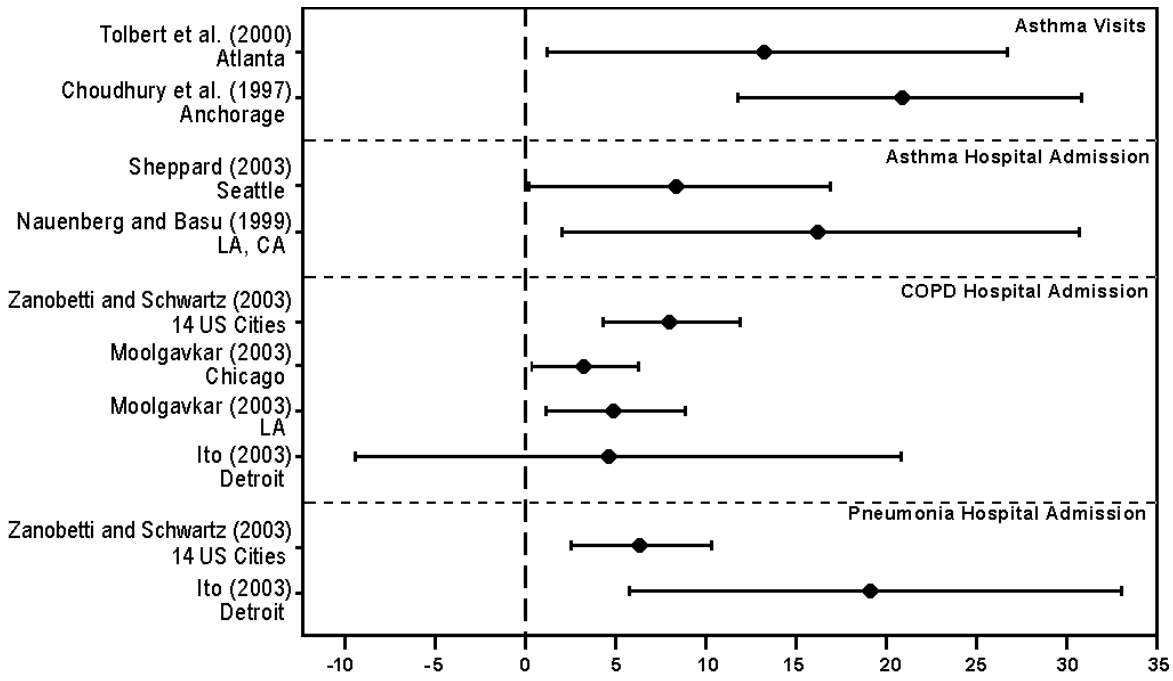

Figure 8-14. Maximum excess risk of respiratory-related hospital admissions and visits per 50 μg/m^3 PM_{10} increment in selected studies of U.S. cities based on single-pollutant models.

Various new medical visits studies (including non-hospital physician visits) indicate that the use of hospital admissions alone can greatly understate the total clinical morbidity effects of air pollution. Thus, these results support the hypothesis that considering only hospital admissions and ED visit effects may greatly underestimate the numbers of medical visits occurring in a population as a result of acute ambient PM exposure. Those groups identified in these morbidity studies as most strongly affected by PM air pollution are older adults and the very young.

8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to ambient concentrations of PM_{10}. The populations studied included several different subgroups (e.g., children, asthmatics,

etc.); and the models used for analysis varied, but did not include GAM use. The pulmonary function studies were suggestive of short-term effects resulting from ambient PM exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min per 50 $\mu g/m^3$ increase in 24-h PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups, e.g., asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies, less numerous than the acute studies, had were inconclusive results.

8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms

The available acute respiratory symptom studies discussed in the 1996 PM AQCD included several different endpoints, but typically presented results for upper respiratory symptoms, lower respiratory symptoms, or cough. These respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

The earlier studies of morbidity health outcomes of PM exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) reported on respiratory symptoms in two panels of Utah Valley asthmatics. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness (LRI) and the second panel of 21 subjects aged 8 to 72 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, found a relationship of shortness of breath to O_3 and PM_{10}, but could not separate effects of the two pollutants (Ostro et al., 1995). These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Numerous new studies of short-term PM exposure effects on lung function and respiratory symptoms published since 1996 were identified by an ongoing Medline search. Most of these followed a panel of subjects over one or more time periods and evaluated daily lung function and/or respiratory symptom in relation to changes in ambient PM_{10}, $PM_{10-2.5}$, and/or $PM_{2.5}$. Some used other measures of airborne particles, e.g. ultrafine PM, TSP, BS, and sulfate fraction of

ambient PM. Lung function was usually measured daily, with most studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF), measured both in the morning and afternoon. Various respiratory symptoms were measured, e.g., cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Detailed summaries of these studies are presented in Appendix 8B. Data on physical and chemical aspects of ambient PM levels (especially for PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and smaller size fractions) are of particular interest, as are new studies examining health outcome effects and/or exposure measures not much studied in the past.

Specific studies were selected for summarization based on the following criteria:

- Peak flow was used as the primary lung function measurement of interest.
- Cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as measures of respiratory symptoms when available.
- Quantitative relationships were estimated using PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and/or smaller PM as independent variables.
- Analyses used in the study were done such that each individual served as their own control.

8.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects

Appendix B Tables 8B-4 and 8B-5 summarize salient features of new studies of short-term PM exposure effects on lung function and respiratory symptoms, respectively, in asthmatic subjects; and key quantitative results are summarized in Table 8-23 for PM_{10} and Table 8-24 for $PM_{2.5}$. The peak flow analyses results for asthmatics tend to show small decrements for PM_{10} and $PM_{2.5}$ as seen in studies by Gielen et al. (1997), Peters et al. (1997b), Romieu et al. (1997), and Pekkanen et al. (1997).

The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. For PM_{10}, the available point estimates for morning PEF lagged one day showed decreases, but the majority of the studies were not statistically significant (as per Table 8-23 and as shown in Figure 8-15 as an example of PEF outcomes). Lag 1 may be more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies which provided such data. The results were consistent for both AM and PM peak flow analyses. Effects using two- to five-day lags averaged about the same as did the zero to one-day lags, but

TABLE 8-23. SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m^3 PM_{10} INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m^3 PM_{10}
Asthma Studies					
Pekkanen et al. (1997)	Morning PEFR	14 (10, 23)	NO_2	0 day	−2.71 (−6.57, 1.15)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	1 day	1.39 (−0.57, 3.35)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	1 day	−4.70 (−7.65, -1.70)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	1 day	−0.65 (−5.32, 3.97)
Peters et al. (1997a)	Morning PEFR	47 (29, 73)	SO_2, sulfate, H^+	1 day	−0.84 (−1.62, −0.06)
Peters et al. (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)
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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-23 (cont'd). SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m^3 PM_{10} INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m^3 PM_{10}
Asthma Studies (cont'd)					
Peters et al. (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 PFT CHANGES IN ASTHMATICS PER 25 µg/m^3 $PM_{2.5}$ INCREMENT

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 $PM_{2.5}$
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)

DRAFT-DO NOT QUOTE OR CITE

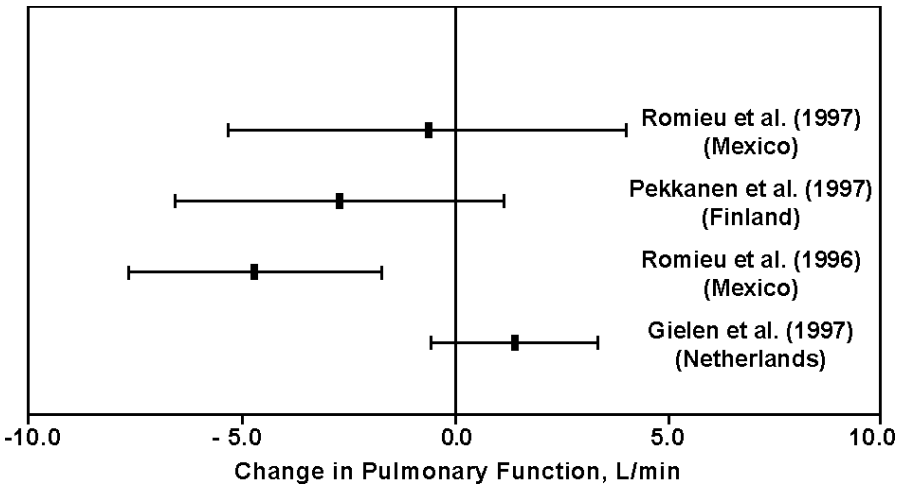

Figure 8-15. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 µg/m^3 PM_{10} on morning Peak flow lagged one-day.

had wider confidence limits. Similar results were found for the fewer $PM_{2.5}$ studies. Of these, Pekkanen et al. (1997) and Romieu et al. (1996) found similar results for $PM_{2.5}$ and PM_{10}, while the study of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$.

Pekkanen et al. (1997) also reported changes in peak flow to be related to several sizes of PM with PN 0.032-0.10 −0.970 (0.502) l(cm^3) and $PM_{1.0-3.2}$ −0.901 (0.536) and PM_{10} −1.13 (0.478) for morning PEF lag 2. Peters et al. (1997c) report that the strongest effects on peak flow were found with ultrafine particles: $PM_{MC\ 0.01-0.1}$: −1.21 (−2.13, −0.30); $PM_{MC0.01-2.5}$: −1.01 (−1.92, −0.11); and PM_{10}, −1.30 (−2.36, −0.24). Penttinen et al. (2001) using biweekly spirometry over 6 months on a group of 54 adult asthmatics found that FVC, FEV_1, and spirometric PEFR were inversely, but mostly nonsignificantly-associated with ultra fine particle concentrations. Compared to the effect estimates for self-monitored PEFR, the effect estimates for spirometric PEFR tended to be larger. The strongest associations were observed in the size range of 0.1 to 1 µm. In a further study, von Klot et al. (2002) evaluated 53 adult asthmatics in Erfurt, Germany in the winter of 1996-1997. Relationships were estimated from generalized estimating equations, adjusting for autocorrelation. Asthma symptoms were related to small particles (MC 0.1-0.5, MC 0.01-2.5) and $PM_{2.5-10}$. The strongest relations were for 14 day mean PM levels, especially for the smaller particles (MC 0.01-2.5).

Overall, then, PM_{10} and $PM_{2.5}$ both appear to affect lung function in asthmatics, but there is only limited evidence for a stronger effect of fine versus coarse fraction particles; nor do ultrafine particles appear to have any notably stronger effect than other larger-diameter fine particles. Also, of the studies provided, few if any analyses were able to clearly separate out the effects of PM_{10} and $PM_{2.5}$ from other pollutants.

The effects of PM_{10} on respiratory symptoms in asthmatics tended to be positive, although they are somewhat less consistent than PM_{10} effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant for PM_{10} (see Tables 8-25, 8-26, 8-27, and 8-28; and, for cough as an example, see Figure 8-16). Vedal et al. (1998) reported that (a) increases in PM_{10} were associated with increased reporting of cough, phlegm production, and sore throat and (b) children with diagnosed asthma are more susceptible to the effects than are other children. Similarly, in the Gielen et al. (1997) study of a panel of children, most of whom had asthma, low levels of PM increased symptoms and medication use. The Peters et al. (1997c) study of asthmatics examined particle effects by size and found that fine particles were associated with increases in cough, of which MC 0.01-2.5 was the best predictor.

Delfino et al. (1998) used an asthma symptom score to evaluate the effects of acute air pollutant exposures. The 1- and 8-hr PM_{10} maximum concentrations had larger effects than the 24-hr mean. Subgroup analyses showed effects of current day PM maxima to be strongest in the 10 more frequently symptomatic children; the odds ratios for adverse symptoms from 90^{th} percentile increases were 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 PM_{10}. Analyses suggested that effects of O_3 and PM_{10} were largely independent. Delfino et al. (2002) also studied 22 asthmatic children aged 9-19 years in March and April 1996. Relationships were evaluated by use of generalized estimating equations, adjusting for autocorrelation. The endpoint was symptoms interfering with daily activities. This endpoint was associated with PM_{10}, NO_2, and ozone. There was a positive interaction effect of PM_{10} and NO_2 jointly.

Romieu et al. (1996) found children with mild asthma to be more strongly affected by high ambient levels of PM (mean PM_{10} = 166.8 $\mu g/m^3$) observed in northern Mexico City than in a study (Romieu et al., 1997) conducted in a nearby area with lower PM_{10} levels (mean PM_{10} = 54.2 $\mu g/m^3$). Yu et al. (2000) reported estimates of odds ratios for asthma symptoms and

TABLE 8-25. SUMMARY OF ASTHMA PM_{10} COUGH 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					
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	1.21 (1.10, 1.33)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	0 day	1.27 (1.16, 1.42)
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	2 day	1.40 (1.13, 1.73)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	2 day	2.19 (0.47, 10.24)
Segala et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	2 day	(values not given because not significant)
Neukirch et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	3 day	(values not given because not significant)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	2 day	1.27 (1.07, 1.50)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	2 day	1.00 (0.92, 1.10)
Ostro et al. (2001)	OR cough	47 (11, 119) 24 hr	Ozone, NO_2	3 day	1.32 (1.12, 1.55)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	0.94 (0.82, 1.08)
Peters et al. (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)

DRAFT-DO NOT QUOTE OR CITE

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 PM_{10} LOWER RESPIRATORY ILLNESS (LRI) STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range)	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-28. SUMMARY OF ASTHMA PM_{10} BRONCHODILATOR USE 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}
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)

DRAFT-DO NOT QUOTE OR CITE

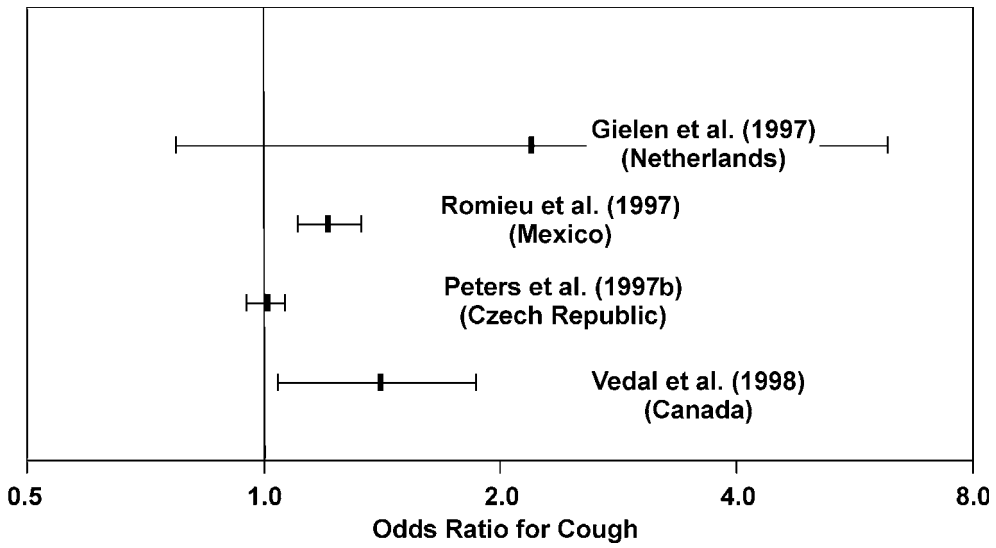

Figure 8-16. Odds ratios with 95% confidence interval for cough per 50-µg/m^3 increase in PM_{10} for selected asthmatic children studies at lag 0.

10 µg/m^3 increments in PM_{10} and $PM_{1.0}$ values of 1.18 (1.05, 1.33) and 1.09 (1.01, 1.18), respectively. Multipollutant models with CO and SO_2 yielded 1.06 (0.95, 1.19) for PM_{10}, and 1.11 (0.98, 1.26) for $PM_{1.0}$, thus showing a lower value for PM_{10} and a loss of significance for both PM_{10} and $PM_{1.0}$. The correlation between CO and $PM_{1.0}$ and PM_{10} was 0.82 and 0.86. Ostro et al. (2001) studied a panel of inner-city African American children using a GEE model with several measures of PM, including PM_{10} (both 24-hour average and 1-hour max.) and $PM_{2.5}$, demonstrating positive associations with daily probability of shortness of breath, wheeze, and cough.

Just et al. (2002) studied 82 asthmatic children for 3 months during spring and early summer in Paris. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. No significant relationships were found between PM_{13} and lung function or respiratory symptoms. Desqueyroux et al. (2002) studied 60 adult severe asthmatics from November 1995 to November 1996. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. PM_{10} was not related to incident asthma attacks using lags of 1 or 2 days; but PM_{10} associations for 3, 4, and 5 day lags were significant. PM_{10} remained significant even after adjusting for other pollutants including O_3, SO_2, and NO_2.

For $PM_{2.5}$ results, see Table 8-29. All showed positive associations (several being clearly significant at $p < 0.05$) between $PM_{2.5}$ and increased cough, phlegm, or LRI. Of studies that included two indicators for PM (PM_{10}, $PM_{2.5}$) in their analyses, the study of Peters et al. (1997c) found similar effects for the two PM measures, whereas the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$.

TABLE 8-29. SUMMARY OF ASTHMA $PM_{2.5}$ RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 µg/m³ $PM_{2.5}$
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)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	0 day	1.04 (0.86, 1.20)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	2 day	1.16 (0.98, 1.33)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	2 day	1.24 (1.02, 1.51)
Ostro et al. (2001)	OR cough	40.8 (4, 208)	Ozone, NO_2	3 day	1.02 (0.98, 1.06)
Peters et al. (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)

Two asthma studies, both in the United States, examined PM indicators by 1 hr averages as well as by 24 hr averages. The PM_{10} 1 hr outcome was larger than the 24 hr outcome for lower respiratory illness in one study (Delfino et al., 1998) but was lower for cough in the other study (Ostro et al., 2001).

Several of the studies reviewed above (Delfino et al., 1998, 2002; Ostro et al., 2001; Yu et al., 2000; Mortimer et al., 2002; Vedal et al., 1998) that were conducted in the United States and Canada found positive associations between various health endpoints for asthmatics and ambient PM exposure (indexed by PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$). The endpoints included PEF decrements, various individual respiratory symptoms, and combinations of respiratory symptoms. The various endpoints each represent effects on respiratory health.

8.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects

Results for PM_{10} peak flow analyses in non-asthmatic studies (summarized in Appendix 8B Table 8B-6) were inconsistent, with fewer studies reporting results in the same manner as for the asthmatic studies. Many of the point estimates showed increases rather than decreases (see Table 8-30). The effects on respiratory symptoms in non-asthmatics (see Appendix 8B Table 8B-7) were similar to those in asthmatics. Most studies showed that PM_{10} increases cough, phlegm, difficulty breathing, and bronchodilator use, although these were generally not statistically significant (Table 8-31). Vedal et al. (1998) reported no consistent evidence for adverse health effects in a nonasthmatic control group.

Results of the $PM_{2.5}$ peak flow and symptom analyses in non-asthmatic studies (see Appendix 8B Table 8B-8, Table 8-32) were similar to PM_{10} results discussed above.

Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999), used $PM_{10-2.5}$ as a coarse fraction particulate measure (Table 8-33). Schwartz and Neas (2000) found that $PM_{10-2.5}$ was significantly related to cough. Tiittanen found that one day lag of $PM_{10-2.5}$ was related to morning PEF, but there was no effect on evening PEF. Neas et al. found no effects of $PM_{10-2.5}$ on PEF.

The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle effects on healthy school children using two pollutant models of fine and coarse PM. CM was estimated by subtracting $PM_{2.1}$ from PM_{10} data. They report for cough for reanalysis of the Harvard Six City Diary Study in the two PM pollutant model $PM_{2.5}$ OR = 1.07 (0.90, 1.26; per 15 $\mu g/m^3$ increment) and $PM_{10-2.5}$ OR 1.18 (1.04, 1.34; per 8 $\mu g/m^3$ increment) 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). In the Uniontown reanalysis, peak flow for $PM_{2.1}$ for a 14 $\mu g/m^3$ increment was –0.91 1/m

TABLE 8-30. SUMMARY OF NON-ASTHMA PM_{10} PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m³ PM_{10}
Gold et al. (1999)	Morning PEFR	51 (23, 878)	Ozone	1 day	−0.20 (−0.47, 0.07)
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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-31. SUMMARY OF NON-ASTHMA PM_{10} RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 mg/m^3 PM_{10}
Schwartz & Neas (2000)	OR cough – no other symptoms	(not given)	Sulfate fraction	0 day	1.20 (1.07, 1.35)
Boezen et al. (1998)	OR cough	42 (5, 146)	NO_2, SO_2	0 day	1.06 (0.93, 1.21)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	0 day	1.04 (0.95, 1.14)
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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-32. SUMMARY OF NON-ASTHMA $PM_{2.5}$ RESPIRATORY OUTCOME STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 μg/m³ $PM_{2.5}$
Gold et al. (1999)	Morning PEFR	30.3 (9, 69)	Ozone	1 day	−0.22 (−0.46, 0.01)
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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8-33. SUMMARY OF NON-ASTHMA COARSE FRACTION STUDIES OF RESPIRATORY ENDPOINTS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m^3	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 μg/m^3 $PM_{10-2.5}$
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)

DRAFT-DO NOT QUOTE OR CITE

(−1.14, −1.68) and $PM_{10-2.1}$ for 15 μg/m^3 +1.04 1/m (−1.32, +3.4); for State College $PM_{2.1}$ −0.56 (−1.13, +0.01) and $PM_{10-2.1}$ −0.17 (−2.07, +1.72).

Coull et al. (2001) reanalyzed data from the Pope et al. (1991) study of PM effects on pulmonary function of children in the Utah Valley, using additive mixed models which allow for assessment of heterogeneity of response or the source of heterogeneity. These additive models describe complex covariate effects on each child's peak expiratory flow while allowing for unexplained population heterogeneity and serial correlation among repeated measurements. The analyses indicate heterogeneity among that population with regard to PM_{10} (i.e., specifically that there are three subjects in the Utah Valley study who exhibited a particularly acute response to PM_{10}). However the limited demographic data available in the Utah Valley Study does not explain the heterogeneity in PM sensitivity among the school children population.

Two studies examined multipollutant models. The Jalaludin et al. (2000) analyses used a multipollutant model that evaluated PM_{10}, O_3, and NO_2. They found in metropolitan Sydney that ambient PM_{10} and O_3 concentrations are poorly correlated (r = 0.13). For PEFR the β (SE) for PM_{10} only was 0.0045 (0.0125), p = 0.72; and for PM_{10} and O_3, 0.0051 (0.0124), p = 0.68. Ozone was also unchanged in the one- and two-pollutant models. Gold et al. (1999) attempted to study the interaction of $PM_{2.5}$ and O_3 on PEF in Mexico City children (age = 8 to 12 yrs). The authors found independent effects of the two pollutants, but the joint effect was slightly less than the sum of the independent effects.

8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

8.3.3.2.1 Summary of 1996 Particulate Matter Air Quality Criteria Document Key Findings

In the 1996 PM AQCD, the available long-term PM exposure-respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a similar type of respiratory symptom questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio

= 1.66) in the community with the highest particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

Interpretation of such studies requires caution in light of the usual difficulties ascribed to cross-sectional studies. That is, evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient, but it was not readily possible to separate out clear effects of PM from other factors or pollutants having the same gradient.

Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from airborne particle pollution indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study of U.S. and Canadian children found significant associations between FEV_1 and FVC and acidic particles (H^+). Overall, the available studies provided only limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.). However, it was noted that cross-sectional studies require very large sample sizes to detect differences because they cannot eliminate person to person variation, which is much larger than the within person variation.

8.3.3.2.2 New Studies of Respiratory Effects of Long-Term Particulate Matter Exposure

Several studies published since 1996 evaluated effects of long-term PM exposure on lung function and respiratory illness (see Appendix 8B, Table 8B-8). The new studies examining PM_{10} and $PM_{2.5}$ in the United States include McConnell et al. (1999), Abbey et al. (1998), Berglund et al. (1999), Peters et al. (1999a,b), and Avol et al. (2001), all of which examined effects in California cohorts but produced variable results. McConnell et al. (1999) noted that, as PM_{10} increased across communities, the bronchitis risk per interquartile range also increased, results consistent with those reported by Dockery et al. (1996). However, the high correlation of PM_{10}, acid, and NO_2 precludes clear attribution of the McConnell et al. bronchitis effects specifically to PM alone. Avol et al. (2001) reported that, for 110 children that moved to other locations 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 higher PM_{10} showed slowed lung function growth.

Gauderman et al. (2000, 2002) presented results from a study that is both a cohort and a cross-sectional study. This unique design followed two cohorts of southern California children who were fourth graders in 1993 and 1996 respectively. The cohorts, located in 12 communities, were followed for 4 years. A three stage model which allowed for individual slopes, within community covariates, and community-wide air pollution averages, was fitted using SAS Proc MIXED. Pulmonary function measurements included FVC, FEV1, MMEF, and PEFR, all of which gave similar results for both $PM_{2.5}$ and PM_{10}. In the first cohort, PM_{10} showed a significant 1.3% decrease in annual growth rates for a 51.5 $\mu g/m^3$ difference in PM_{10}. This difference was only 0.4% in the second cohort; however, the two were not significantly different from each other. The effect for $PM_{2.5}$ was slightly less for a difference of 22.2 $\mu g/m^3$. Peters et al. (1999b) studied the prevalence of respiratory symptoms in 12 southern California communities in 1993. To estimate the relationship between symptoms and pollutants a two-stage regression approach was used. The first stage estimated community-specific rates adjusted for individual covariates. The second stage regressed these rates on pollutant averages from 1986 to 1990, finding no significant relationships between respiratory symptoms and average PM_{10} levels.

In a non-U.S. PM_{10} study, Horak et al. (2002) conducted a combined cohort and cross-sectional study similar in design to that of Gauderman et al. (2000). The cohorts were taken from 975 school children in 8 communities in lower Austria between 1994-1997. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. Adjustments were made for sex, atopy, ETS, baseline lung function, height, and site. Growth in FVC and MEF were significantly related to winter PM_{10} levels.

Gehring et al. (2002) enrolled 1,756 newborn children in the Munich area. Individual $PM_{2.5}$ and NO_2 levels were estimated from actual measurements at 40 sites combined with a GIS predictor model. $PM_{2.5}$ levels ranged from 11.9 to 21.9 $\mu g/m^3$. The incidence (in the first two years of life) of cough without infection and dry cough at night were related to $PM_{2.5}$ levels. Wheeze, bronchitis, respiratory infections, and runny nose were not related to $PM_{2.5}$ levels.

Other non-U.S. studies examined PM measures such as TSP and BS in European countries. In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted

twice (with the same 971 children included in both surveys). TSP levels decreased between surveys as did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer et al. (1999) reported a study in six East and West Germany communities, which found decreasing yearly TSP levels to be related to ever-diagnosed bronchitis from 1991-1995. Lastly, Jedrychowski et al. (1999) reported an association between both BS and SO_2 levels in various areas of Krakow, Poland, and slowed lung function growth (FVC and FEV_1).

Leonardi et al. (2000) studied a different health outcome measure as part of the Central European Air Quality and Respiratory Health (CESAR) study. Blood and serum samples were collected from school children ages 9-11 yrs. in each of 17 communities in Central Europe (N = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations increased across the cities. Regression slopes, adjusted for confounder effects, were largest and statistically significant for $PM_{2.5}$, but small and non-significant for $PM_{10-2.5}$. A similar positive relationship was found between IgG concentration in serum and $PM_{2.5}$ gradient, but not for PM_{10} or $PM_{10-2.5}$. These results tend to suggest a PM effect on immune function more strongly due to ambient fine particle than coarse particle exposure.

8.3.3.2.3 Summary of Long-Term Particulate Matter Exposure Respiratory Effects

The methodology used in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to PM) while others reported no significant results. The cross-sectional studies are often confounded, in part, by unexplained differences between geographic regions. The studies that looked for a time trend are also confounded by other conditions that were changing over time. The newer studies that combine the features of cross-sectional and cohort studies provide the best evidence for chronic effects. These studies include Peters et al. (1999b), Gauderman et al. (2000), and Gauderman et al. (2002). The Gauderman studies found significant decreases in lung function growth among So. California school children to be related to PM_{10} levels. However, Peters et al. (1999b) found no relationship between respiratory symptoms and annual average PM_{10} levels in 12 So. California communities.

The cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), assessed before in the previous 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle acidity.

8.4 DISCUSSION OF EPIDEMIOLOGIC STUDIES OF HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER

8.4.1 Introduction

Numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely contributor to mortality and morbidity effects associated with ambient air pollution exposures. Since preparation of the 1996 PM AQCD, the epidemiologic evidence concerning ambient PM-related health effects has vastly expanded. Past regulatory decisions have been important in the selection of PM indices and evolution of PM epidemiologic literature. That is, the adoption of PM_{10} standards in 1987 and of $PM_{2.5}$ standards in 1997 have generated ambient air concentration databases that have made it possible for research to address many previously unresolved issues regarding possible linkages between airborne PM and human health; and the newly authorized nationwide network of speciation samplers holds promise for further advances regarding identification of the most influential specific components of the ambient air pollution mixture and their sources.

As was discussed in Sections 8.2 and 8.3, numerous new PM epidemiology studies, both of short-term and long-term PM exposure, have yielded findings indicating that statistically significant excess risks for various mortality and/or morbidity endpoints in many U.S. cities and elsewhere are associated with ambient PM indexed by a variety of ambient community monitoring methods.

Still, several uncertainties discussed in the 1996 PM AQCD continue to be important in assessing and interpreting the overall PM epidemiology database and its implications for estimating risks associated with exposure to ambient PM concentrations in the United States: (1) potential confounding of PM effects by co-pollutants (especially major gaseous pollutants such as O_3, CO, NO_2, SO_2); (2) the attribution of PM effects to specific PM components (e.g., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafines, sulfates, metals, etc.) or source-oriented indicators (motor vehicle emissions, vegetative burning, etc.); (3) the temporal relationship between exposure and effect (lags, mortality displacement, etc.); (4) the general shape of exposure-response relationship(s) between PM and/or other pollutants and observed health effects (e.g., potential indications of thresholds for PM effects); and (5) the consequences of measurement error. All of these modeling issues are of much importance and interest in selection of appropriate statistical models for characterizing and interpreting ambient PM-health effects associations.

Assessing the above uncertainties in relation to the PM epidemiology data base remains a challenge. The basic issue is that there are an extremely large number of possible models, any of which may turn out to give the best statistical "fit" of a given set of data, and only some of which can be dismissed *a priori* as biologically or physically illogical or impossible, except that putative cause clearly cannot follow effect in time. Most of the models for daily time-series studies are fitted by adjusting for changes over long time intervals and across season, by day of week, weather, and climate. Many of the temporal and weather variable models have been fitted to data using semi-parametric methods such as spline functions or local regression smoothers (LOESS). The goodness of fit of these base models has been evaluated by criteria suitable for generalized linear models (GLM) with Poisson or hyper-Poisson responses (number of events) with a log link function, particularly the Akaike Information Criterion (AIC) and the more conservative Bayes information criterion (BIC), which adjust for the number of parameters estimated from the data. The Poisson over-dispersion index and the auto-correlation of residuals are also often used. It is often assumed, but rarely proven, that the best-fitting models with PM would be models with the largest and most significant PM indices. However, if high correlations between PM and one or more gaseous pollutants emitted from a common source (e.g., motor vehicles) exist in a given area, then disentangling their relative individual partial contributions to observed health effects associations becomes very difficult. There have been very few attempts at broad, systematic investigations of the model selection issue and little reporting of goodness-of-fit criteria among competing models that represent one approach by which to assess or compare models.

Substantial prior knowledge to guide model fitting now exists and an informed modeling strategy can yield a useful set of models as one type of sensitivity analysis. To illustrate, a systemic evaluation of model choice has been carried out by Clyde et al. (2000), using Bayesian Model Averaging for the same Birmingham, AL, data as analyzed by Smith et al. (2000). Several different calibrated information criterion priors were tried in which models with large numbers of parameters are penalized to various degrees. After taking out a baseline trend (estimated using a GLM estimate with a 30-knot thin-plate smoothing spline), 7,860 models were selected for use in model averaging. These included lags 0-3 days of a daily monitor PM_{10}, an area-wide average PM_{10} value with the same lags, temperature (daily extremes and average) lagged 0-2 days, humidity (dewpoint, relative humidity min and max, average specific humidity)

lagged 0-2 days, and atmospheric pressure, lagged 0-2 days. The model choice is sensitive to the specification of calibrated information criterion priors, in particular disagreeing as to whether different PM_{10} variables should be included or not. For example, one or another PM_{10} variable is included in all the top 25 Akaike Information Criterion (AIC) models, but only in about 1/3 of the top Bayes Information Criterion (BIC) models. Both approaches give a relative risk estimate of about 1.05, with credibility intervals of (0.94, 1.17) for the AIC prior and (0.99, 1.11) for the BIC prior. A validation study in which randomly selected data were predicted using the different priors favored Bayesian model averaging with BIC prior over model selection (picking the best model) with BIC or any approach with AIC. This type of modeling may represent another type of multi-pollutant modeling approach in addition to more typical hypotheses-driven model construction and interpretation that draws more on external information (e.g., exposure, dosimetric, toxicologic relationships) in specifying models and interpreting their results.

The possibility that an observed effect is "real" (i.e., likely to be found in an independent replication of the study) or merely a statistical artifact is usually characterized by its confidence interval or by its estimated significance level. In most of this document, confidence intervals, or credible intervals for Bayesian analyses, are reported in order to emphasize that the effect size is not known with certainty, but some values are more nearly consistent with the data than effect size values outside the interval. P-values or t-values are implicitly associated with a null hypothesis of no effect. A nominal significance level of $p \leq 0.05$ or 5% (i.e., a 95% confidence interval) is usually used as a guide for the reader, but P-values should not be used as a rigid decision-making tool. If the observed confidence intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider.

Given the now extremely large number of published epidemiologic studies of ambient PM associations with health effects in human populations and the considerably wide diversity in applications of even similar statistical approaches (e.g., "time-series analyses" for short-term PM exposure effects), it is neither feasible nor useful here to try to evaluate the methodological soundness of every individual study. Rather, a three-pronged approach is likely to yield useful evaluative information: (1) an overall characterization of evident general commonalities (and/or notable marked differences) among findings from across the body of studies dealing with particular PM exposure indices and types of health outcomes, looking for convergence of

evidence regarding types of effects and effect-sizes attributable to ambient PM indices across various methodologically acceptable analyses; (2) thorough, critical assessment of newly published multi-city analyses of PM effects, assuming that greater scientific weight is generally ascribable to their results than those of smaller-sized studies (often of individual cities) yielding presumably less precise effect size estimates; and (3) evaluation of coherence of the findings among different types of effects and across various geographic locations, as well as with other types of pertinent biological information (e.g., exposure, dosimetry, toxicity, etc.).

In the sections that follow, issues noted above are critically discussed. In addition, given that both the newer multi-city study results and those of newer single-city analyses tend to show evidence of somewhat greater geographical heterogeneity in estimated PM risks across cities and regions than had been seen in studies assessed in the 1996 PM AQCD, the issue of geographical heterogeneity in PM effect estimates is further evaluated here.

First follows a discussion of the GAM issue and a summary of some key findings emerging from the short communications and peer-review commentary recently published by HEI (2003).

8.4.2 GAM Issue and Reanalyses Studies

As discussed earlier, Dominici et al. (2002) reported that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate in all cases. The actual importance of this effect has only recently begun to be quantified, the results of recent reanalyses of many key studies being especially helpful in this regard; those reanalyses are described in short communicatons published in the HEI (2003b) Special Report. As for the net outcome of these reanalyses efforts, HEI (2003b) summarizes it well, as follows:

> Overall, the revised analyses using GAM with more stringent convergence criteria and iterations and GLM-natural splines resulted in lower estimates, but largely confirmed the effect of exposure to particulate matter on mortality (Burnett and Goldberg, 2003; Dominici et al., 2003; Katsouyanni et al., 2003; Samoli et al. ,2003; Schwartz, 2003b; Zanobetti and Schwartz, 2003a) and morbidity, especially for hospitalizations for cardiovascular and respiratory diseases (Atkinson et al., 2003; Fairley, 2003; Gold et al., 2003; Hoek, 2003; Ito, 2003; Le Tertre et al., 2003; Ostro et al., 2003; Schwartz, 2003a; Sheppard, 2003; Zanobetti and Schwartz, 2003b). As in earlier analyses, the effect was more pronounced among individuals 65 years of age and older (Fairley; Gold et al.; Goldberg and Burnett; Ito; Le Tertre et al.; Mar et al.; Mooigavkar; Schwartz a). The impact of various sensitivity analyses,

when these were performed, differed across the studies. No significant impacts were seen in some (Ostro et al.), whereas in others, alternative modeling of time (Klemm and Mason; Moolgavkar) and weather factors (Goldberg and Burnett; Ito) resulted in substantial changes.

The following discussion evaluates in more detail the nature and extent of potential problems in the various studies that have used the GAM default algorithm, but which have also had their analyses redone using alternative methods unaffected by this convergence issue.

8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Mortality

Many of the reanalysis studies analyzed associations between PM_{10} and mortality, allowing an examination of the impact of GAM convergence problem on this PM index. Table 8-34 and Figure 8-17 shows the percent excess total non-accidental mortality (unless noted otherwise) risk estimates per 50 $\mu g/m^3$ increase in PM_{10} derived from the reanalysis studies for (1) GAM with default convergence criteria; (2) GAM with stringent convergence criteria; and, (3) GLM with natural splines that approximate the original GAM model. The figure shows results only from the studies that used all of the three alternative models for PM_{10}. It can be seen that most, but not all, reanalyses resulted in reductions in PM_{10} risk estimates when more stringent convergence criteria were used in GAM models. Using GLM with natural splines resulted in additional reduction in PM_{10} risk estimates for most, but not all, cases. The extent of reductions in PM_{10} risk estimates in GAM with more stringent convergence criteria or GLM with natural splines was in most cases less than 1% excess deaths per 50 $\mu g/m^3$ increase in PM_{10}. Obviously, the relative reduction is greater for the studies that had smaller PM_{10} risk estimates in the original analyses (e.g., NMMAPS U.S. 90 cities analyses). It can also be seen from Figure 8-17 that the extent of reduction in PM_{10} risk estimates is smaller compared to the variability of PM_{10} risk estimates across the studies. Thus, the effect of the GAM convergence problem does not appear, in most cases, to be substantial. Potential factors affecting the heterogeneity of PM_{10} risk estimates across studies are discussed in later sections. Several of the reanalysis reports also analyzed $PM_{2.5}$ and $PM_{10-2.5}$. Generally, the pattern and extent of reductions in mortality risk estimates were similar to those for PM_{10}. The results and a comparison of $PM_{2.5}$ and $PM_{10-2.5}$ mortality risk estimates are presented in a later section.

TABLE 8-34. PM_{10} EXCESS RISK ESTIMATES FROM REANALYSIS STUDIES FOR TOTAL NON-ACCIDENTAL MORTALITY PER 50 μg/m^3 INCREASE IN PM_{10}

Study	GAM-default	GAM-stringent	GLM
NMMAPS 90-cities; Dominici et al. (2002)	2.1 (1.6, 2.6)	1.4 (0.9, 1.9)	1.1 (0.5, 1.7)
Harvard 6-cities; Klemm and Mason (2003)	4.1 (2.8, 5.4)	3.6 (2.1, 5.0)	2.0 (0.3, 3.8)
US 10 cities; Schwartz (2003b)	3.4 (2.7, 4.1)	3.3 (2.6, 4.1)	2.8 (2.0, 3.6)
8 Canadian cities; Burnett and Goldberg (2003)	4.5 (2.2, 6.7)	3.6 (1.4, 5.8)	2.7 (−0.1, 5.5)
APHEA2; Katsouyanni et al. (2003)	3.5 (2.9, 4.1)	3.3 (2.8, 3.9)	2.1 (1.5, 2.8)
Santa Clara Co.; Fairley (2003)	8.0 (no interval given)	7.8 (2.8, 13.1)	8.3 (2.9, 13.9)
Coachella Valley; Ostro et al. (2003)*	5.6 (1.7, 9.6)	5.5 (1.6, 9.5)	5.1 (1.2, 9.1)
Los Angeles Co.; Moolgavkar (2003)	2.4 (0.5, 4.4)	2.4 (0.5, 4.3)	2.3 (0.1, 4.5)
Cook Co.; Moolgavkar (2003)	2.4 (1.3, 3.5)	2.6 (1.6, 3.6)	2.6 (1.5, 3.7)
Phoenix, AZ; Mar et al. (2003)*	9.9 (1.9, 18.4)	9.7 (1.7, 18.3)	9.5 (0.6, 19.3)
Detroit, '85-'90; Ito (2003)	1.7 (0.2, 3.2)	0.9 (−0.5, 2.4)	0.7 (−0.8, 2.1)
Detroit, '92-'94; Ito (2003)	4.4 (−1.0, 10.1)	3.3 (−2.0, 8.9)	3.1 (−2.2, 8.7)
The Netherlands; Hoek (2003)	0.9 (0.1, 1.7)	0.9 (0.2, 1.7)	0.9 (0.1, 1.7)
Erfurt, Germany; Stolzel et al. (2003)	6.4 (0.3, 12.9)	6.2 (0.1, 12.7)	5.3 (−1.8, 12.9)

*Cardiovascular Mortality

Dominici et al. (2002) also illustrated that GAM models, even with stringent convergence criteria, still result in biased (downward) standard errors of regression coefficients. This was the main reason for the use of GLM with natural splines in the reanalysis studies. As can be seen from Figure 8-17, the 95% confidence bands are somewhat wider for GLM results than for GAM results in some, but not all cases. However, the extent of wider confidence bands is not substantial in most cases (the bias ranged from a few percent to ~15% in most cases). It should be noted that, while a GLM model with natural splines provides correct standard error of regression coefficient, it is not equivalently as flexible as LOESS or smoothing splines. Unlike LOESS or smoothing splines, natural splines fit linearly at both ends of the data span. Natural splines therefore may not be an ideal model option for temperature effects, for which the slopes are likely non-linear (especially at the higher end). Goldberg and Burnett (2003), in their reanalysis of Montreal data, discussed related issues. In their reanalysis, the originally reported

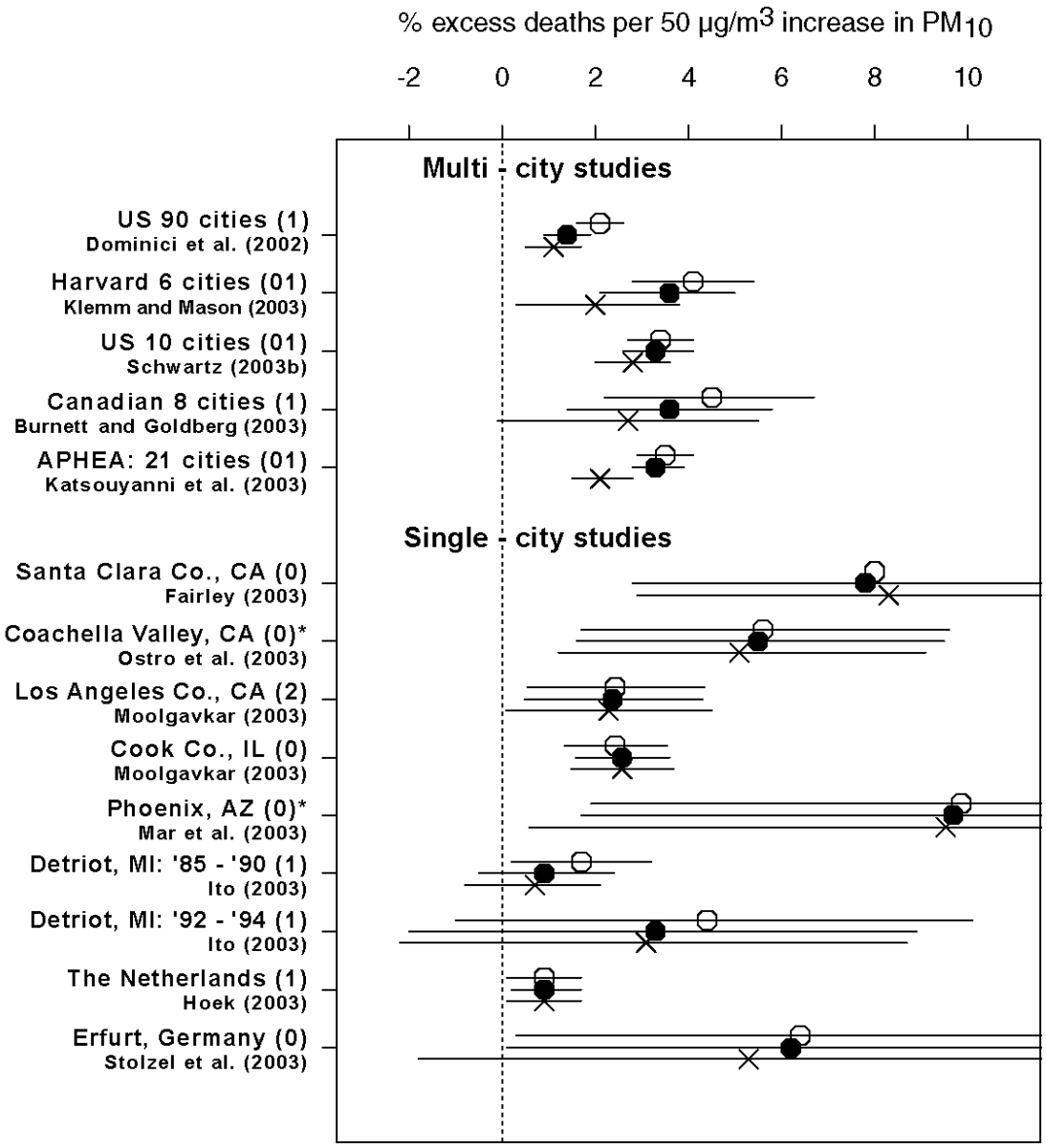

Figure 8-17. PM_{10} excess risk estimates for total non-accidental mortality for numerous locations (and for cardiovascular mortality[*] for Coachella Valley, CA and Phoenix, AZ), using: (1) GAM with default convergence criteria (white circle); (2) GAM with stringent convergence criteria (black circle); and, (3) GLM/natural splines (x) that approximate the original GAM model from the GAM reanalysis studies. The numbers in parenthesis indicate lag days used ("01" is average of 0 and 1 day lags).

risk estimates of PM indices (CoH, extinction coefficient, predicted $PM_{2.5}$, and sulfate) were greatly attenuated in the GLM model with natural splines. One of the alternative explanations for these results was that the natural spline does not fit the possibly non-linear (threshold) effect of temperature as well as non-parametric smoothers. Hoek (2003), in his reanalysis of the Netherlands data, also showed that, compared to GAM models, GLM/natural spline models resulted in larger deviance, indicating poorer fits. Thus, there are remaining issues regarding the trade-off between GAM/non-parametric smoothers and GLM/parametric smoothers. The GLM/natural splines may produce correct standard errors but cannot guarantee "correct" model specifications. More recently, Dominici et al. (2003) developed and published a GAM routine for SPlus that gives correct standard errors, but it was not developed in time to be used for the GAM reanalysis effects reported on in HEI (2003b).

Three reanalysis reports applied alternative smoothing approaches (e.g., penalized splines) that, as with GLM/natural splines, did not have the problem of biased standard error. These studies were: reanalyses of Harvard six cities data by Schwartz (2003a); reanalysis of 10 US cities data by Schwartz (2003b); and reanalysis of APHEA2 by Katsouyanni et al. (2003). Generally, as with GLM/natural splines, the use of alternative smoothing approaches resulted in smaller PM risk estimates than GAM with stringent convergence criteria. In the re analysis of APHEA2 study, the PM_{10} risk estimates from penalized splines were smaller than those from GAM model, but larger than those from natural splines. Three alternative smoothing approaches (B-splines, penalized splines, and thin-plate splines) used in the reanalysis of Harvard six cities $PM_{2.5}$ data resulted in generally smaller risk estimates than those from natural splines. As was expected, all of these alternative smoothing approaches resulted in standard errors that were comparable to those from natural splines but larger than those from GAM models.

Several of the GAM reanalysis reports included additional sensitivity analyses which provided useful information. These sensitivity analyses included examinations of the effect of changing degrees of freedom for smoothing of temporal trends and weather variables (Dominici et al. [2002]; Ito [2003]; Klemm and Mason [2003]; Moolgavkar [2003]; and Burnett and Goldberg [2003]). In these analyses, changing the degrees of freedom for smoothing of temporal trends or weather effects often resulted in change of PM coefficients to a similar or even greater extent than those caused by the GAM convergence problem. A distinctly less well investigated issue is the effect of the use of different weather model specifications (i.e., how

many weather variables and their lags are included). In a limited examination of this issue in the reanalysis of Detroit data (Ito, 2003), a weather model specification similar to that used in the US 90 cities consistently resulted in smaller PM_{10} risk estimates than a weather model similar to that used in Harvard six cities study.

In summary, the results from the GAM reanalysis studies indicate that PM risk estimates from GAM models were often, but not always, reduced when more stringent convergence criteria were used. However, the extent of the reduction was not substantial in most cases. The variability of PM risk estimates due to the model specification, including the number of weather terms and extent of smoothing, is likely larger than the effect of the GAM convergence problem. The extent of downward bias in standard error reported in these data (a few percent to ~15%) also appears not to be very substantial, especially when compared to the range of standard errors across studies due to differences in population size and numbers of days available. Still, the discussions in this chapter focus mainly on the reanalyzed studies or the studies that did not use GAM with default convergence criteria, because the extent of the effect of this problem is not always predictable in each individual study.

8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Respiratory Hospital Admissions

The NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} concentrations and hospital admissions used the default GAM model specification with multiple smooths. To be quantitative in terms of the change that results from the more stringent GAM criteria, Figure 8-18 shows a plot of the respiratory models for which Zanobetti and Schwartz (2003b) provided reanalyses. These results indicate that there was only about a 14% decline in the effect estimates associated with use of the more appropriate stringent convergence requirement. Moreover, it is clear that the two estimates are well within the 95% confidence interval of each other, indicating that the two models are not statistically significantly different from one another.

To examine the potential influence of the GAM convergence specification on the results of the original Detroit data analysis by Lippmann et al. (2000), the associations between PM components and daily mortality/morbidity were re-examined by Ito using more stringent convergence criteria, as well as by applying a GLM that approximated the original GAM models (Ito, 2003). Generally, the GAM models with stringent convergence criteria and GLM models

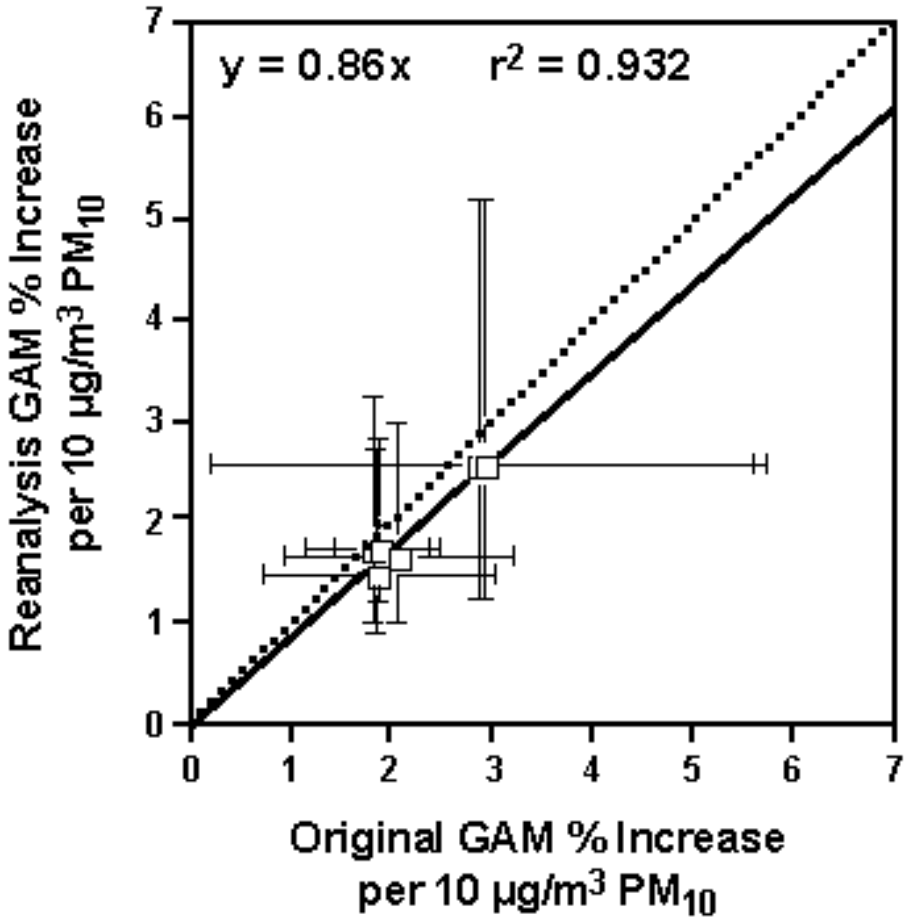

Figure 8-18. Comparison of GAM results for original (default) convergence case versus those from reanalyses with a more stringent convergence criterion (10e-15) for constrained lag respiratory model cases. Note very high overall correlation (r = 0.932) of original default GAM values with reanalysis stringent GAM results and slightly greater divergence from $r^2 = 1.0$ (dotted line) as excess risk values per 10 µg/m^3 PM_{10} increase.

Source: Derived from Zanobetti and Schwartz (2003b).

resulted in somewhat smaller estimated relative risks than those reported in the original study, but the reduction is quite small (averaging 17% less for the stringent GAM case versus default). For COPD, the decrease associated with the more stringent convergence criteria is larger (averaging 30%). Overall, for all types of hospital admissions (including pneumonia, COPD and ischemic heart disease) the effect of the change to the more stringent GAM gave an average

decrease of 20 percent, while a switch to the GLM model specification gave an average 29% decrease in estimated PM effect size.

As discussed earlier, Sheppard (2003) recently conducted a reanalysis of their non-elderly hospital admissions data for asthma in Seattle, WA, in order to evaluate the effect of the fitting procedure on their previously published analyses. A lag of 1 day was used for all PM models. As shown in Table 8-35, the results were provided in the manuscript to only one significant figure (to the nearest whole percent), making the calculation of percent changes between models problematic, since the rounding of the effect estimates are nearly of the order of the size of the effect estimate changes. However, it can be seen that the pattern of changes in effects estimates and 95% CI values is similar to that seen in other studies.

TABLE 8-35. COMPARISON OF MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} FOR SEATTLE ASTHMA HOSPITAL ADMISSIONS BASED ON ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS REANALYSES USING GAM WITH MORE STRINGENT CONVERGENCE CRITERIA AND GLM

	Original Default GAM Model* % Increase/IQR (95% CI)	Reanalysis Stringent GAM % Increase/IQR (95% CI)	Reanalysis GLM (Natural Spline) % Increase/IQR (95% CI)
$PM_{2.5}$	4 (2, 7)	4 (1, 6)	3 (1, 6)
$PM_{2.5-10}$	4 (1, 7)	2 (0, 5)	2 (−1, 4)
PM_{10}	5 (2, 8)	4 (1, 7)	3 (0, 6)

*$PM_{2.5}$ IQR=11.8 ug/m^3; $PM_{2.5-10}$ IQR = 9.3 ug/m^3; PM_{10} IQR = 19 ug/m^3.

Source: Derived from Sheppard (2003).

Further evidence of the relatively small effect of the default convergence criteria issue in most applications is the recent work by Moolgavkar (2003), in which he reanalyzed his earlier GAM analyses of hospital admissions for COPD (Moolgavkar, 2000c) for the cities of Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models. In the same study, similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found

in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0-19 yr; 20-64 yr) in Los Angeles, as well. In his reanalyses of these GAM results using the more stringent convergence criteria, however, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect of using the more stringent convergence criteria on the results. In the case of the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing the more stringent convergence criteria, so direct before/after comparisons were not possible for Moolgavkar's Chicago reanalyses.

Therefore, in order to provide a one-to-one comparison for Los Angeles, the original age-specific GAM analyses have been pooled using inverse variance weighting and are presented along with Moolgavkar's (2003) reanalyses results (in terms of a % increase per 10 $\mu g/m^3$ mass increase for both $PM_{2.5}$ and PM_{10}) in Table 8-36. As shown in that table, the Moolgavkar Los Angeles results for all-age COPD admissions for the original and the more stringent convergence criteria GAM cases (using the same degrees of freedom) are very similar, with the effects estimate either decreasing (for $PM_{2.5}$) or increasing (for PM_{10}) very slightly. In those cases where a much larger number of degrees of freedom were used with either the more stringent GAM model or a natural spline GLM model, larger reductions in effects estimates were obtained as compared to the original GAM model. For the same number of degrees of freedom, the natural spline model resulted in either a slightly larger (for $PM_{2.5}$) or a slightly smaller (for PM_{10}) effects estimate than the stringent GAM model. Thus, these reanalysis results indicate that the use of the more stringent GAM convergence criteria results in minimal changes to the size of the PM effect estimates in this case, as compared to those obtained using the default GAM model, whereas the number of degrees of freedom used with either GAM or GLM models can result in much larger changes in the size of the PM effects estimates. More specifically, use of the much larger number of degrees of freedom results in a much less efficient estimate of the pollutant effect.

These various reanalyses results therefore confirm that the PM effect estimates generally do decline somewhat when using the more stringent convergence criteria, as compared to the default GAM, with the new estimates being well within the confidence interval of the original estimates. In addition, the effect of using a more stringent convergence criteria was indicated to

TABLE 8-36. COMPARISON OF LOS ANGELES COPD HOSPITAL ADMISSIONS MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$ and PM_{10} FROM THE ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS FOR REANALYSES USING MORE STRINGENT CONVERGENCE CRITERIA AND FOR MODELS SMOOTHED WITH MORE DEGREES OF FREEDOM

	Original Default GAM Model* (30df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Stringent GAM (30df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Stringent GAM (100df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Natural Spline (100df) % Increase/10 ug/m^3 (95% CI)
$PM_{2.5}$	1.90 (0.97-2.84)**	1.85 (0.82-2.89)**	1.38(0.51-2.25)***	1.49(0.41-2.58)***
PM_{10}	1.43 (0.85-2.02)**	1.51 (0.85-2.18)**	1.08 (0.50-1.66)**	0.98 (0.24-1.72)**

*Original GAM estimates derived for "all ages" from original analyses by age subgroups using inverse variance weights.
**For (maximum) lag case = 2 days.
***For (maximum) lag case = 0 days.

Source: Derived from Moolgavkar (2000c) and Moolgavkar (2003).

have less influence on the effect estimate than potential investigator-to-investigator variations in model specifications (e.g., extent of smoothing) can have. Overall, the absolute effect was relatively small, and the basic direction of effect and conclusions regarding the significance of the PM effect on hospital admissions remained unchanged in these analyses when the GAM convergence requirement was made more stringent.

8.4.2.3 HEI Commentaries

The HEI Special Report (2003a,b) presents the HEI Special Panels' reviews of both the Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study, Part II (NMMAPS) and the Revised Analyses of Selected Time-Series Studies, which includes short communication reports presenting results from other revised analyses of original articles and reports. Beyond looking at the results of reanalyses designed specifically to address problems associated with the use of default convergence criteria in the S-Plus GAM function, the reviews also identified issues associated with the sensitivity of study findings to the use of alternative modeling approaches that some investigators employed in their reanalyses. In general, the Special Panels concluded that the original PM effects estimates were more sensitive to the

modeling approach used to account for temporal effects and weather variables than to the convergence criteria used in the GAM model.

A modeling issue of particular importance highlighted by HEI (2003b) is the sensitivity of all models (e.g., GAM, GLM-natural splines, GLM-penalized splines) to the degrees of freedom allotted to potentially confounding weather variables and time. The commentary discusses the trade-off involved in selecting the number of degrees of freedom for time and weather variables, while recognizing that there remains no altogether satisfactory way to choose the most appropriate degrees of freedom. For example, in considering the effect of temperature, if the degrees of freedom in the smoothing function for temperature are overly restricted, some actual nonlinear effects of temperature would be falsely ascribed to the pollution variable. To avoid this, the analyst is tempted to afford many degrees of freedom to temperature or other potentially confounding variables. However, if more degrees of freedom are allotted than needed, such that the temperature smooth function is more "wiggly" than the true dose response function, then the result will be a much less efficient estimate of the pollutant effect. This would have the effect of incorrectly ascribing part of the true pollution effect to the temperature variable, which would compromise our ability to detect a true but small pollution effect. The commentary notes that the empirical data cannot determine the optimal trade-off between these conflicting needs, and it is difficult to use an a priori biological or meteorologic knowledge to determine the optimal trade-off. Thus, the Special Panel generally recommends further exploration of the sensitivity of these studies to a wider range of alternative degrees of smoothing and to alternative specifications of weather variables in time-series models.

More specifically, the Specials Panels offered the following conclusions and recommendations:

NMMAPS Revised Analyses

Dominici et al. (2002) conducted a range of revised analyses, applying alternative methods to correct shortcomings in the S-Plus GAM programming. HEI's Special Panel review (HEI, 2003a) of this revised analyses yielded the following conclusions:

- While estimates of effect are quantitatively smaller than those in the original studies, a statistically significant overall effect of PM_{10} on mortality remains, and the qualitative conclusions that were initially drawn from NMMAPS remain unchanged.

- While the alternative approaches used to model temporal effects in the revised NMMAPS analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the preprogrammed GAMs software, no models can be recommended at this time as being strongly preferred over another for use in this context.
- While formal tests of PM effect across cities did not indicate evidence of heterogeneity because of the generally large individual-city effect standard errors, the power to assess the presence of heterogeneity was low. The possibility of heterogeneity still exists.
- The appropriate degree of control for time in these time-series analyses has not been determined. Thus, the impact of more aggressive control for time should continue to be explored and studies to evaluate bias related to the analytic approach to smoothing and the degree of smoothing should be encouraged.
- Weather continues to be a potential confounder of concern, such that further work should be done on modeling weather-related factors.

Revised Analyses for Other Short Communications

Based on its review, the HEI Special Panel (HEI, 2003b) reached the following conclusions:

- As was the case with the findings of the original studies, the revised findings will continue to help inform regulatory decisions regarding PM.
- The PM effect persisted in the majority of studies, however, the number of studies showing an adverse effect of PM was slightly smaller.
- In some of the large number of studies in which the PM effect persisted, the estimates of PM effect were substantially reduced.
- In the few studies in which further sensitivity analyses were performed, some showed marked sensitivity of the PM effect estimate to the degree of smoothing and/or the specification of weather.
- The use of more appropriate convergence criteria on the estimates of PM effect in the revised analyses produced varied effects across the studies. In some studies, stricter convergence criteria had little impact, and in a few the impact was substantial. No study's

conclusions changed in a meaningful way by the use of stricter criteria compared to the original analyses.

- In most studies, parametric smoothing approaches used to obtain correct standard errors of the PM effect estimates produced slightly larger standard errors than the GAM. However, the impact of these larger standard errors on level of statistical significance of the PM effect was minor.
- For the most part, the original PM effect estimates were more sensitive to the method used to account for temporal effects than to changing the convergence criteria.
- Even though the alternative approaches used to model temporal effects in the revised analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the GAMs software, none can be recommended at this time as being strongly preferred over another for use in this context.
- Neither the appropriate degree of control for time nor the appropriate specification of the effects of weather in these time-series analyses has been determined. This awareness introduces a degree of uncertainty that has not been widely appreciated previously, such that the sensitivity of these studies to a wider range of alternative degrees of smoothing and alternative specifications of weather variables in time-series models should continue to be explored.

8.4.3 Assessment of Confounding by Co-Pollutants

8.4.3.1 Introduction

Airborne particles are found among a complex mixture of atmospheric pollutants, some of which are well measured (such as gaseous criteria co-pollutants O_3, CO, NO_2, SO_2) and others which are not routinely measured. The basic question here is one of determining the extent to which observed health effects can be attributed to airborne particles acting alone or in combination with other air pollutants. Many of the pollutants are closely correlated due to emissions by common sources and dispersion by common meteorological factors, so that it may be difficult to disentangle their effects (as noted in Section 8.1.1), because some are in the pathway of formation of other pollutants (e.g., NO $\rightarrow$ NO_2 $\rightarrow$ NO_3^{-1} $\rightarrow$ Particle Mass).

It is widely accepted that some PM metrics are associated with health effects, and that PM has effects independent of the gaseous co-pollutants. The extent to which ambient gaseous co-pollutants may have health effects independent of PM is important in considering the extent to which health effects attributed to PM may actually be due in part to co-pollutants or to some other environmental factors, and vice versa. EPA produces Air Quality Criteria Documents for four gaseous pollutants: CO, NO_2, SO_2, and O_3 (U.S. Environmental Protection Agency, 1982, 1996b, 2000b). The possible health effects of the gaseous pollutants exerted independently from PM, and in some cases jointly with PM, are discussed in those documents. They are also considered to some extent in this section and elsewhere in this document because they may affect quantitative assessments of the effects of various PM metrics when these other pollutants are also present in the atmosphere. The gaseous pollutants may also be of interest as PM effect modifiers, or through interactions with PM.

Co-pollutant models have received a great deal of attention in the last few years because there now exist improved statistical methods for estimating PM effects by analyses of daily time-series of mortality (Schwartz and Marcus, 1990; Schwartz, 1991) or hospital admissions (Schwartz, 1994) and/or in prospective cohort studies (Dockery et al., 1993). A number of studies using the new methods have not only found significant positive relationships between mortality and one or more PM indicators, but also with one or another of the four gaseous criteria pollutants (O_3, NO_2, CO, SO_2) in daily time-series studies, and between SO_2 and mortality in the reanalyses of two large prospective cohort studies (Krewski et al., 2000). In the daily time-series studies, the estimated PM effect is relatively stable when the co-pollutant is included in the model in some cities, whereas the estimated PM effect in other cities changes substantially when certain co-pollutants are included. In the Krewski et al. (2000) analyses, the estimated effect of $SO_4^=$ is greatly decreased when SO_2 is also included as a predictor in a proportional hazards model. A number of the analyses presented below also discuss models in which multiple particle metrics are present, either with or without the gaseous criteria pollutants. These mixtures are encountered in urban air. Included among the studies evaluating both fine and coarse particles are the following ones: Burnett et al. (2000), Chock et al. (2000), Clyde et al. (2000), Fairley (1999), Lippmann et al. (2000), Mar et al.(2000), Cifuentes et al. (2000), and Castillejos et al. (2000).

Carbon monoxide, NO_2, and SO_2 may be acting as indicators of distinct emission sources (e.g., motor vehicle exhaust coal- or oil-burning electric power plants, etc.) and/or as indicators of PM from these sources (primary particles and secondary nitrate particles). Concentrations of such gaseous co-pollutants may therefore be correlated with total PM mass, and they may be even more strongly correlated with specific PM constituents due to their emission from a common source. Thus, one or another specific gaseous co-pollutant may serve as an indicator of the day-to-day variation in the contribution of a distinct emission source and to the varying composition of airborne PM. In a model with total PM mass, then, a gaseous co-pollutant may well actually serve as a surrogate for the source-apportioned contribution to ambient air PM. It would be interesting to evaluate models that include both source-relevant particle components and gaseous pollutants derived from common sources (e.g., those attributable to motor vehicles, coal combustion, oil combustion, etc.). The closest approach so far has been Model II in Burnett et al. (2000), a default GAM analyses.

The role of gaseous pollutants as surrogates for source-apportioned PM may be distinct from confounding. The true health effect may be independently associated with a particular ambient PM constituent that may be more or less toxic than the particle mix as a whole. Thus, a gaseous co-pollutant may give rise to the appearance of confounding in a regression model. By serving as an indicator of the more toxic particles, the gaseous co-pollutant could greatly diminish the coefficient for total particle mass. In such a model, the coefficient for total particle mass would most properly be interpreted an indicator of the other, less-toxic particles.

8.4.3.2 Conceptual Issues in Assessing Confounding

Two main conceptual issues are encountered in evaluating potential confounding: (a) biological plausibility and (b) exposure plausibility. These concerns overlap two of Hill's (1965) suggested criteria for causal inference.

(a) Biological plausibility: It is generally accepted that O_3, NO_2, and SO_2 are associated with diminished pulmonary function and increased respiratory symptoms as well as more serious consequences, and CO exposure has been associated with cardiovascular effects. While one may question whether adverse health effects occur in most healthy people at current exposure to ambient concentrations, there may be susceptible sub-populations for whom one or more ambient gaseous pollutants could perhaps cause health effects at currently encountered ambient

exposure levels. Thus, one should not necessarily assume, a priori, that the gaseous co-pollutants at current ambient levels are not associated with respiratory and cardiovascular health effects in susceptible subpopulations. Nor should the converse be assumed without further evaluation.

Ambient gaseous co-pollutants can be potential confounders of ambient PM only if: (a) both the gas and PM are able to cause the same health effects; (b) if personal exposure is correlated with ambient concentrations for both particles and gases respectively; (c) if the personal exposure to gases and to particles are correlated, and; (d) if the ambient concentrations of particles and gases are correlated.

(b) Exposure plausibility: While most Americans spend most of their time in indoor microenvironments, there is still sufficient personal exposure to O_3 to cause notable respiratory symptoms among sensitive children or adults exercising outdoors when ambient O_3 concentrations are high (hence the declaration of "ozone alert" days). It is also likely that some fraction of ambient CO can contribute to indoor air pollution and total personal CO exposure. Nitrogen dioxide, while reactive, also penetrates indoors; and an ambient pollution component of total personal exposure to NO_2 can be identified among individuals without indoor NO_2 sources but living close to strong outdoor sources such as highways. While there may be some, perhaps many, individuals exposed to elevated concentrations of gaseous criteria pollutants, in order for them to contribute to health effects shown to be associated with ambient concentrations of another given co-pollutant (e.g., PM), the ambient gaseous pollutants must be significantly and positively correlated with the exposure to that co-pollutant.

8.4.3.3 Statistical Issues in the Use of Multi-Pollutant Models

Multi-pollutant models may be useful tools for assessing whether the gaseous co-pollutants may be *potential* confounders of PM effects, but cannot determine if in fact they are. Variance inflation and effect size instability can occur in non-confounded multipollutant models as well as in confounded models. Our usual regression diagnostic tools can only determine whether there is a potential for confounding. In PM epidemiology studies, the gaseous pollutants, except ozone, frequently have a high degree of positive linear correlation with PM metrics, a condition known as multi-collinearity; therefore, although multi-colinearity leading to effect size estimate

instability and variance inflation are necessary conditions for confounding, they are not sufficient in and of themselves to determine whether confounding exists.

The most commonly used methods include multi-pollutant models in which both the putative causal agent (PM) and one or more putative co-pollutants are used to estimate the health effect of interest. If the effect size estimate for PM is "stable," then it is often assumed that the effects of confounding are minimal. "Stable" is usually interpreted as meaning that the magnitude of the estimated effect is similar in models with PM alone and in models with PM and one or more co-pollutants, and the statistical significance or width of the confidence interval for the PM effect is similar for all models, with or without co-pollutants. These criteria (usually unquantified) diagnose confounding in a narrow sense, interpreted as synonymous with multi-collinearity, not as a failure of the study design or other forms of model mis-specification.

Beyond the conceptual issues discussed above that arise in assessing confounding, there are a number of technical issues that arise in the use of statistical models. Those issues are discussed below.

(a) Model mis-specification assumes many forms. The omission of predictive regressors ("underfitting", defined by Chen et al., 2000) may produce biased estimates of the effects of truly predictive regressors that are included in the model. Inclusion of unnecessary or non-predictive regressors along with all truly predictive regressors ("over-fitting") will produce unbiased estimates of effect, but may increase the estimated standard error of the estimated effect if it is correlated with other predictors. Omitting a truly predictive regressor while including a correlated but non-causal variable ("mis-fitting") will attribute the effect of the causal regressor to the non-causal regressor. Interaction terms are candidates for omitted regressor variables. It is important to avoid the "mis-fitting" scenario. Assuming that there is a linear relationship when the true concentration-response function is non-linear will produce a biased estimate of the effect size, high or low at different concentrations. One of the most common forms of model mis-specification is to use the wrong set of multi-day lags, which could produce any of the consequences described as "under-fitting" (e.g., using single-day lags when a multi-day or distributed lag model is needed), "over-fitting" (e.g., including a longer span of days than is needed), or "mis-fitting" (e.g., using a limited set of lags while the effects are in fact associated with different set of lags). Different PM metrics and gaseous pollutants may have

different lag structures, so that in a multi-pollutant model, forcing both PM and gases to have the same lag structure is likely to yield "mis-fitting." Finally, classical exposure measurement errors (from use of proxy variables) attenuates (biases) effect size estimates under most assumptions about correlations among the regressors and among their measurement errors (Zeger et al., 2000).

(b) Bias: All of the mis-specifications listed in (c) can bias the effect size estimate except for "over-fitting" and measurement error of Berkson type. The estimates of the standard error of the effect size estimate under "over-fitting" or Berkson error cases are inflated, however; and result in broader confidence intervals than would otherwise occur with a more appropriately specified model and/or one with less Berkson type measurement error.

(c) Estimates of effect size standard errors are usually sensitive to model mis-specification. When all truly predictive regressors are added to an "underfit" model, the uncertainty will almost always be reduced sufficiently that the standard errors of estimated effect size are reduced ("variance deflation"). Adding correlated non-causal variables to "over-fitted" or "mis-fitted" models will further increase the estimated standard errors ("variance inflation"). Variance inflation can occur whenever a covariate is highly correlated with the regressor variable that is presumably the surrogate for the exposure of interest. Confounding with the regressor variable can occur only when the covariate is correlated (a) with the regressor variable proxy for the exposure of interest and (b) with the outcome of interest in the absence of the exposure of interest.

(d) Mis-specification errors may compound each other. If the concentration-response function is nonlinear but there is measurement error in the exposures, then different sub-populations will have greater or smaller risk than assigned by a linear model. Consider the hypothetical case of a "hockey-stick" model with a threshold. If there were no exposure measurement error, then the part of the population with measured concentrations above the threshold would have excess risk, whereas those below would not. If exposures were measured with error, even if the measured concentration were above the threshold, some people would actually have exposures below the threshold and no excess risk. Conversely, if the measured

concentration was below the threshold, some people would actually have concentrations above the threshold and would have excess risk. The flattening of a non-linear concentration-response curve by measurement error is a well known phenomenon that may be detected by standard methods (Cakmak et al., 1999).

(e) The question of whether effect size estimates and their standard errors are really significantly different among models is usually not addressed quantitatively. Some authors report various goodness-of-fit criteria such as AIC, BIC, deviance, or over-dispersion index, e.g., (Chock et al., 2000; Clyde et al., 2000), but the practice is not yet so wide-spread as to assist in analyses of secondary data for use in this document. Variance inflation may also happen with a correctly specified model when both pollutants are causal and highly correlated, compared to a model in which only one pollutant is causal and the non-causal pollutant is omitted. The situation where the variance or standard error decreases when an additional variable is added (variance deflation) suggests that the model with the covariate is more nearly correct and that the standard errors of all covariates may decrease. Statistical significance is a concept of limited usefulness in assessing or comparing results of many models from the same data set. Still, it is a familiar criterion, and one addressed here by using a nominal two-sided 5% significance level for all tests and 95% confidence intervals for all estimates, acknowledging their limitations. There is at present no consensus on what clearly constitutes "stability" of a model estimate effect size, e.g., effect sizes that differ by no more than 20% (or some other arbitrary number) from the single-pollutant models. Simple comparison of the overlap of the confidence intervals of the models is not used because the model estimates use the same data, and the confidence intervals for effect size in different models are more-or-less correlated. In analyses with missing days of data for different pollutants, comparisons must also incorporate differences in sample size or degrees of freedom.

In any case, statistical comparisons alone cannot fully resolve questions about either conceptual or statistical issues in confounding via considerations about statistical significance. If the model is mis-specified in any of the numerous ways described above, then effect size estimates and/or their estimated standard errors are likely biased. Statistical assessments alone can determine if the PM metric is too closely correlated with other pollutants to allow for a reasonably accurate quantitative effect size estimate (which is, of course, useful information

even if it is concluded that it is not feasible to estimate the separate effects of PM and/or the gaseous co-pollutants). However, no matter what the statistical situation, confounding cannot occur if the gaseous co-pollutant(s) cannot produce the health outcome, or if there is no personal exposure to the gaseous co-pollutant(s), or if that personal exposure is not correlated with their ambient concentrations.

The most commonly used approach to diagnose potential confounding is fitting multi-pollutant models and evaluating the stability of the estimated particle effect sizes against inclusion of co-pollutants. If an additional covariate is added to a baseline model (e.g., with PM alone) and the model predicts the outcome better with the covariate, then the reduction in variance (or deviance for generalized linear or additive models [GLM or GAM]) outweighs the loss of degrees of freedom for variability. Although not always true, it is reasonable to expect a decrease in the estimated asymptotic standard error of the effect size estimate ("variance deflation"), but improved goodness-of-fit may not reduce the standard errors of all parameters in equal proportion because introducing the new covariate modifies the covariate variance-covariance matrix. The weighted inverse covariance matrix provides an exact estimate for standard errors in ordinary linear regression models, and approximately so in GLM or GAM. The effects on other parameter estimates are rarely reported.

"Variance inflation" may occur under several circumstances, including "under-fitting" and "mis-fitting" in which a truly predictive covariate is omitted or replaced by a correlated proxy, and "over-fitting" in which a non-predictive covariate correlated with the PM metric is also included in the model. The potential for over-fitting can be diagnosed by evaluating the eigenvalues of the correlation matrix of the predictors, with very small values identifying near-collinearity. However, the complete covariate correlation matrix is almost never reported, including all weather variables and nonlinear functions entered separately as covariates. Nonetheless, even a correlation matrix among all pollutants would be informative. Furthermore, composite correlation matrices in multi-city studies may conceal important differences among the correlation matrices.

Multi-pollutant models may be sensitive to multi-colinearity (high correlations among particle and gaseous pollutant concentrations) and to so-called "measurement errors", possibly associated with spatial variability. Combining multi-pollutant models across several cities may not improve the precision of the mean PM effect size estimate combined, if the differences

among the cities are as large or larger in the multi-pollutant models as in the single-pollutant PM model. Second-stage regressions have been useful in identifying effect modifiers in the NMMAPS and APHEA 2 studies, but may not, in general, provide a solution to the problem that confounding of effects is a within-city phenomenon. Furthermore, the correlations among pollutants may change from season to season and from place to place, suggesting that confounding as indicated by co-linearity is not always the same.

Three promising alternative approaches versus simple reliance on multi-pollutant modeling have begun to be used to evaluate more fully and definitively the likelihood that exposures to gaseous co-pollutants can account for the ambient PM-health effects associations now having been reported in hundreds of published epidemiology studies. The first is based on evaluation of personal exposures to particles and gases as was done for three panels of participants in Baltimore, MD (Sarnat et al., 2000, 2001). This study (discussed in detail in Chapter 5) directly addresses the premise that if individuals are not exposed to a potential confounder, then it cannot really be a confounder of the presumed causal effect. The results in this paper support the conclusion that personal exposure to sulfates, fine particles, and PM_{10} are well correlated with their corresponding fixed site ambient concentrations, but the correlations are much lower for $PM_{10-2.5}$, O_3, and NO_2. There is however a great deal of variation from one of three two-week panels from one season to the next. The sample size is small (N = 56), but did detect marginally significant associations between personal and ambient NO_2 for the personal-ambient correlation, although much lower than for particles. There were, however, a number of residences in which personal and ambient NO_2 were highly correlated. This has been known to happen in other studies when the residences are close to a major road, which was the case for several members in each of the three studied cohorts (i.e, health elderly adults, adults with COPD, and children 9-13 years).

An other promising approach is the use of principal component or factor analysis to determine which combinations of gaseous criteria pollutants and PM size fractions or chemical constituents together cannot be easily disentangled, and which pollutants are substantially independent of the linear combinations of the others. For example, the source-oriented factor analysis study of Mar et al. (2000) produced evidence suggesting independent effects of regional sulfate, motor vehicle-related particles, particles from vegetive burning, and PM_{10-25} for cardiovascular mortality in Phoenix (as discussed in Section 8.2.2.4.3).

There are also now available some recent examples of a third promising approach, i.e., the use of so-called "intervention studies." Particularly interesting evidence for independent effects of ambient PM beginning to emerge from such studies, which relate changes (decreases in health risk outcomes) to decreases in airborne particles due to deliberate reductions in emissions from sources that ordinarily contribute to elevated ambient PM levels in a given locale. As described in the next subsection (8.4.3.4), the PM-health outcome changes occurred in the presence of low concentrations of ambient gaseous co-pollutants or little change in at least some of the co-pollutants in the presence of the reduced concentrations of PM mass or constituents.

8.4.3.4 Epidemiologic Studies of Ambient Air Pollution Interventions

To date, investigations of health risk in epidemiologic studies of ambient air pollutants, including PM, have relied largely on studies that focus on increases in exposure and that evaluate whether health risk changes occur in relation to such increases. Such studies are used to support qualitative and quantitative inferences as to whether decreases in exposure will bring about reductions in health risk, or improvement in health status.

Ambient criteria air pollutants are rarely, if ever, the only etiology of the health disorders with which exposures to these pollutants are associated. For example, numerous reports have implicated ambient air pollution exposure with exacerbations of pre-existing asthma. These reports justify the expectation that further reduction in ambient air pollution exposure would reduce the public health burden of asthma exacerbations. However, many other factors, including allergens, passive smoking, exercise, cold, and stress are also associated with such exacerbations. Asthmatics would continue to be exposed to these factors even with further reduction in ambient air pollution exposure. Thus, reduction of ambient air pollution exposure, even to zero concentration, would not bring about zero risk of the health disorders with which such exposure is associated. Also, it is likely that at least some non-pollution risk factors would behave differently in the absence of ambient air pollution exposure as in its presence. That is, in the real world, risk factors probably do not behave in discrete, additive fashion.

Direct quantitative characterization of effects of reduction in air pollution concentrations and exposures requires the study of situations in which such reductions actually occur. In such studies, it is important to measure both exposure and health status before and after exposure is

reduced. It is also highly desirable to identify risk factors other than ambient air pollution, and to ascertain their effects before and after air pollution exposure reduction.

In his classic monograph (The Environment and Disease: Association or Causation?), Hill (1965) addressed the topic of preventive action and its consequences under Aspect 8, stating:

> "Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed."

The available epidemiologic literature on ambient air pollution generally offers only limited evidence related to this aspect. A few pertinent studies have evaluated situations where air pollution concentrations have been temporarily or permanently reduced through regulatory action, industrial shutdown, or other intervening factor(s).

In the U.S., the most thoroughly studied example of such ambient air pollution reduction occurred in the Utah Valley, UT, during the 1980s. The Valley's largest stationary source of PM, a steel mill, was closed due a labor dispute for 13 months from autumn 1986 until autumn 1987. This offered the opportunity to study health effects not only of the closure-related reduction in ambient PM concentrations, but also of the increases in PM that occurred after the re-opening of the mill. Pope et al. have reported extensively on such health effects. The relevant reports having been addressed in detail in the 1996 PM AQCD. Briefly, these investigators observed reduction in frequency of a variety of health disorders during the period in which the mill was closed. These included daily mortality (Pope et al., 1992), respiratory hospital admissions (Pope, 1989), bronchitis and asthma admissions for preschool children (Pope, 1991), reductions in lung function (Pope et al., 1991), and elementary school absences (Ransom and Pope, 1992). Changes in these endpoints were reflected by differing strength of positive associations between measures of these health endpoints and PM mass measurements from filters collected before, during, and after the steel mill shut down.

As discussed in Chapter 7 of this document, several experimental studies investigated effects of aqueous extracts of ambient Utah Valley particulate filters employing filter extracts from January through March 1986 (mill open), 1987 (mill closed), and 1988 (mill open)

(Frampton et al., 1999; Dye et al., 2001; Soukup et al., 2000; Wu et al., 2001; and Ghio and Devlin, 2001). In all of these studies, investigators observed less intense in vivo or in vitro effects when treating with the 1987 (mill closed) extracts than when treating with (mill open) extracts from 1986 and/or 1988. The methodology descriptions provided across the above five papers are somewhat unclear as to the degree of comparability of source filters among these five studies (some being from TSP and others from PM_{10} filters); and there is some uncertainty as to the within-study comparability of filters from year to year, particularly in the studies that employed 34 filters per year. Furthermore, some proportion of the extracted material may have been derived from filter matrix, not ambient PM; and about 10 years elapsed between collection and extraction of the filter samples.

Even so, the combined results of these five experimental studies provide support and corroboration for the epidemiologic observations of reduced frequency and severity of health disorders during the period of steel mill closure during which PM_{10} (and to some extent SO_2) levels were notably reduced, but already relatively low CO, NO_2, and O_3 were much less changed. The experimental studies also provide support for hypotheses regarding potential biological mechanisms underlying some of the observed effects. Perhaps the strongest of these hypotheses is that PM-associated metals were etiologically related to some of the observed disorders, and that reduction in ambient concentrations of these metals was at least partially responsible for the health benefits observed during steel mill closure. In any event, these experimental studies underscore the importance of particle composition in production or promotion of harmful health effects (Beckett, 2001).

Another study (Avol et al., 2001) investigated effects of reductions and increases in ambient air pollution concentrations on longitudinal lung function growth in a subsample of participants in the Children's Health Study conducted by the University of Southern California. Follow-up lung function tests were administered to 110 children who had moved away from the study area after the baseline lung function test, which was administered while the children lived within the study area. Lung function growth rates were analyzed against differences between the children's original and new communities in annual average concentrations of PM_{10}, NO_2, and O_3. Analytical models were adjusted for anthropometric variables and other relevant covariates. No multi-pollutant analyses were reported. Moving to a community with lower ambient PM_{10} concentration was associated with increased growth rates of FVC, FEV1, MMEF and PEFR;

whereas moving to a community with higher PM_{10} concentrations was associated with decreased growth of these metrics. These associations were statistically significant for MMEF and PEFR, and appear to have been marginally significant for FVC and FEV1. Moving to a community with lower ambient NO_2 or O_3 concentration was also generally associated with increased lung function growth, and vice versa; however, the associations of change in lung function growth with change in community levels of NO_2 and O_3 were not statistically significant. This study suggests, most clearly, that reduction in long-term ambient PM_{10} levels is indeed associated with improvement of children's lung growth, and that increase in these levels is associated with retardation of lung growth.

In yet another U.S. study, Friedman et al. (2001) investigated the influence of temporary changes in transportation behaviors (instituted to reduce downtown traffic congestion during the 1996 Summer Olympic Games in Atlanta, GA) on ambient air quality and acute care visits and hospitalizations for asthma in children residing in Atlanta. Ambient air quality and childhood asthma during the 17 days of the Games were compared to those during a baseline period consisting of the four weeks before and the four weeks after the Games. During the Games, concentrations of PM_{10} (24-h average), O_3 (daily peak 1-h average), CO (8-h average), and NO_2 (daily peak 1-h average) were, respectively, 16.1%, 27.9%, 18.5%, and 6.8% lower than during the baseline period. Twenty-four hour average concentrations of SO_2 were 22.1% higher during the Games than during the baseline period. Reductions in O_3, PM_{10}, and CO were statistically significant at alpha = 0.05 ($p = 0.01$, $p < 0.001$, and $p = 0.02$, respectively). Ambient mold counts during the Games did not differ significantly from those during the baseline period. Four sources of asthma frequency data were examined: (1) the Georgia Medicaid claims file; (2) files of a health maintenance organization; (3) emergency department records for two of Atlanta's three pediatric hospitals; and (4) the Georgia Hospital Discharge Database. For all four sources, asthma-related unadjusted and adjusted relative risks during the Games were less than 1 (as compared to RR = 1 during the baseline period). Relative risks from the Medicaid database were statistically significant ($p \leq 0.005$), and those from the HMO approached significance ($p \leq 0.10$). These findings suggest strongly that, in Atlanta in summer 1996, temporary improvement in ambient air quality contributed to temporary reduction in severity of pre-existing asthma. This reduction could not be attributed specifically to any individual air pollutant, but reductions in PM and O_3 would seem to be among the most likely contributors to the observed effect on

asthma visits. In the opinion of Friedman et al., reductions in morning rush-hour traffic played an important role in reduction of asthma-related visits and hospitalizations.

Heinrich et al. (2000) studied the effects of long-term air pollution reduction in the former East Germany on prevalence of respiratory illnesses and symptoms in 5 to 14 year-old children. Cross-sectional surveys were conducted in 1992-1993 and 1995-1996 in three areas, all of which experienced reductions in annual mean ambient SO_2 and TSP concentrations in the time interval between the surveys. Percentage reductions in SO_2 and TSP were substantial, ranging from about 40%-60% and about 20%-35%, respectively, in the three areas. Longitudinal changes were not measured for size-specific PM metrics. After adjustment for relevant covariates, statistically significant temporal decreases in prevalences of bronchitis, otitis media, frequent colds, and febrile infections were observed.

In Hong Kong, a regulation prohibiting the use of fuel oil containing more than 0.5% sulfur by weight went into effect in July 1990. Investigators from the University of Hong Kong studied respiratory health in children and non-smoking women before and after the regulation was implemented. In a relatively polluted district (District A), the regulation resulted in rapid and substantial reduction in the ambient SO_2 concentration and in appreciable, but less marked, reduction in the concentration of sulfate ion in "respirable suspended particulates" (RSP, thought to be equivalent to PM_{10}). Percentage reductions in these sulfur-containing pollutants were considerably smaller in a less polluted district (District B). The regulation was not accompanied by appreciable reductions in levels of PM metrics (TSP and RSP) in either district.

Tam et al. (1994) reported that the prevalence of bronchial hyperreactivity (BHR) in children (as defined by a $\geq$ 20% drop in FEV1 in response to histamine challenge) was higher in District A than in District B, even after exclusion of children with wheeze and asthma. Wong et al. (1998) measured BHR prevalence rates in these districts in 1991 and 1992, and compared these to rates before the regulation was implemented. In both districts, BHR prevalence was statistically significantly lower in 1991 than before the intervention. In 1992, the pre- to post-intervention decrease in BHR prevalence was significantly larger in District A than in District B. Peters et al. reported that before the intervention, prevalences of children's respiratory symptoms (e.g., cough, sore throat, wheeze) were statistically significantly higher in District A than in District B. About one year after the intervention, there were greater pre- to post-intervention declines in prevalences of cough or sore throat, phlegm, and wheezing in District A

than in District B. Wong et al. reported that before the intervention, the prevalence of poor respiratory health in non-smoking women was significantly higher in District A than in District B. Also, effects of passive smoking on the women's respiratory health were stronger in District A than in District B, but not significantly so. About one year after the intervention, declines in frequency of poor respiratory health were observed, but these declines did not differ significantly between districts. Taken together, these Hong Kong studies suggest that reduction of sulfur in fuel oil brought about appreciable improvement in children's respiratory health, and discernible but lesser improvement in non-smoking women's respiratory health. These studies also suggest that these benefits were associated with reduction in sulfur-containing ambient air pollutants, but not necessarily with reduction in TSP or RSP per se.

Taken together, these epidemiologic intervention studies tend to support the conclusion that reductions in ambient air pollution (especially PM) exposures resulted in decreased respiratory and cardiovascular health effects. The available studies also give reason to expect that further reductions in both particulate and gaseous air pollutants would benefit health. On balance, these studies suggest that selective reduction in ambient PM concentrations might well bring about greater benefit than would selective reduction in concentrations of other ambient criteria air pollutants. Furthermore, the experimental studies of Utah Valley filter extracts point to PM-associated metals as a likely cause or promoter of at least some of the health effects associated with ambient PM. Beyond this, available epidemiologic intervention studies do not yet give direct, quantitative evidence as to the relative health benefits that would result from selective reduction of specific PM size fractions. Also, these studies do not yet provide firm grounds for quantitative prediction of the relative health benefits of single-pollutant reduction strategies versus multi-pollutant reduction strategies. Even in an almost ideal “natural experiment” such as Utah Valley, potentially confounding factors other than ambient PM concentrations may have also changed during the steel mill closure. These included changes in concentrations of at least one other pollutants (i.e., SO_2) and possible changes in population due to out- and in-migration influenced by the closing and re-opening of the steel mill. While changes in ambient PM concentrations undoubtedly played a role, other factors may also have modified the size of the changes in health effects.

8.4.4 Role of Particulate Matter Components

In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive associations between ambient PM_{10} concentrations and various health indicators, e.g., mortality, hospital admissions, respiratory symptoms, pulmonary function decrements, etc. Some studies were also then available which mortality and morbidity associations with various fine particle indicators (e.g., $PM_{2.5}$, sulfate, H^+, etc.). One mortality study, the Harvard Six Cities analysis by Schwartz et al. (1996a), evaluated relative contributions of the fine ($PM_{2.5}$) versus the coarse ($PM_{10-2.5}$) fraction of PM_{10}, and found, overall, that $PM_{2.5}$ appeared to be associated more strongly with mortality effects than $PM_{10-2.5}$. A few studies seemed to be indicative of possible coarse particle effects, e.g., increased asthma risks associated with quite high PM_{10} concentrations in a few locations where coarse particles strongly dominated the ambient PM_{10} mix.

8.4.4.1 Fine- and Coarse-Particle Effects on Mortality

A rapidly growing number of new studies published since the 1996 PM AQCD provide an expanded evidence base examining associations of ambient PM with increased human mortality and morbidity risks. As was indicated in Table 8-1, most newly reported analyses, with a few exceptions, continue to show statistically significant associations between short-term (24-h) PM concentrations and increases in daily mortality in many U.S. and Canadian cities (as well as elsewhere). Also, the reanalyses of Harvard Six City and ACS study data substantiate the original investigator's findings of long-term PM exposure associations with increased mortality as well.

8.4.4.1.1 Total Mortality Effects

The effects estimates from the newly reported studies are generally consistent with those derived from the earlier 1996 PM AQCD assessment, which reported risk estimates for excess total (nonaccidental) deaths associated with short-term PM exposures as generally falling within the range of ca. 1 to 8% per 50 $\mu g/m^3$ PM_{10} (24-h) increment and ca. 2 to 6% increase per 25 $\mu g/m^3$ $PM_{2.5}$ (24-h) increment.

Several new PM epidemiology studies which conducted time-series analyses in multiple cities were noted to be of particular interest, in that they provide evidence of effects across various geographic locations (using standardized methodologies) and more precise pooled effect

size estimates with narrow confidence bounds, reflecting the typically much stronger power of such multi-city studies over individual-city analyses to estimate a mean effect. Based on pooled analyses across multiple cities, using GAM stringent convergence criteria, the percent total (non-accidental) excess deaths per 50 $\mu g/m^3$ PM_{10} (24-h) increment were estimated in different multi-city analyses to be: (a) 1.4% in the 90 largest U.S. cities; (b) 3.4% in 10 large U.S. cities; (c) 3.6% in the 8 largest Canadian cities; and (d) 3.0% in European cities.

Many new individual-city studies found positive associations (most statistically significant at $p < 0.05$) for the $PM_{2.5}$ fraction, with effect size estimates for U.S. and Canadian cities typically ranging from ca. 2.0 to ca. 8% per 25 $\mu g/m^3$ $PM_{2.5}$ (although one estimate for cardiovascular mortality ranged up to about 19%). Of the 10 or so new analyses that not only evaluated PM_{10} effects but also compared fine versus coarse fraction contributions to total mortality, only two are multi-city analyses yielding pooled effects estimates: (a) the Klemm and Mason (2000) and Klemm and Mason (2003) recomputation analyses for Harvard Six Cities data, confirming the original findings published by Schwartz et al. (1996a); and (b) the Burnett et al. (2000) and Burnett and Goldberg (2003) studies of the 8 largest Canadian cities. These studies found roughly comparable, statistically significant excess risk estimates for $PM_{2.5}$ (i.e., approximately 2% increased total mortality risk per 25 $\mu g/m^3$ $PM_{2.5}$ increment).

As for possible coarse particle short-term exposure effects on mortality, in those new studies which evaluated $PM_{10-2.5}$ effects as well as $PM_{2.5}$ effects, the coarse particle ($PM_{10-2.5}$) fraction was also consistently positively associated with increased total mortality, albeit the coarse fraction effect size estimates were generally less precise than those for $PM_{2.5}$ and statistically significant at $p < 0.05$ in only a few studies (as can be seen in Figure 8-6). Still, the overall picture tends to suggest that excess total mortality risks may well reflect actual coarse fraction particle effects, in at least some locations. This may be most consistently the case in arid areas, e.g., in the Phoenix area (as shown in Mar et al., 2000 and Mar et al., 2003) or in Mexico City and Santiago, Chile. On the other hand, elevations in coarse PM-related total mortality risks have also been detected for Steubenville, OH (an eastern U.S. urban area in the Harvard Six City Study), as shown by Schwartz et al. (1996a); Klemm et al. (2000), Klemm and Mason (2003). These results may reflect contamination of later-resuspended coarse PM by metals in fine PM emitted from smelters (Phoenix) or steel mills (Steubenville) that was earlier deposited on nearby soils. Excess total mortality risks associated with short-term (24-h)

exposures to coarse fraction particles capable of depositing in the lower respiratory tract generally fall in the range of 0.2 to 6.0% per 25 μg/m^3 PM_{10-25} increment for U.S. and Canadian cities.

Three new papers provide particularly interesting new information on relationships between short-term coarse particle exposures and total elderly mortality (age 65 and older), using exposure TEOM data from the EPA ORD NERL monitoring site in Phoenix, AZ. Each used quite different models but each reported statistically significant relationships between mortality and coarse PM, specifically $PM_{10-2.5}$, an indicator for the thoracic fraction of coarse-mode PM.

Smith et al. (2000), using a three-day running average as the exposure metric, performed linear regression of the square root of daily mortality on the long-term trend, meteorological and PM-based variables. Two mortality variables were used, total (non-accidental) deaths for the city of Phoenix and the same for a larger, regional area. Using a linear analysis, effects based on coarse PM were statistically significant for both regions, whereas effects based on fine PM ($PM_{2.5}$) were not. However, when the possibility of a nonlinear response was taken into account, no evidence was found for a nonlinear effect for coarse PM; but fine PM was found to have a statistically significant effect for concentration thresholds of 20 and 25 μg/m^3. There was no evidence of confounding between fine and coarse PM, suggesting that fine and coarse PM are "essentially separate pollutants having distinct effects". Smith et al. (2000) also observed a seasonal effect for coarse PM, the effect being statistically significant only during spring and summer. Based on a principal component analysis of elemental concentrations, crustal elements are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000) felt that the implication that crustal, rather than anthropogenic elements, were responsible for the PM mortality was counterintuitive.

Clyde et al. (2000) used a more conventional model, a Poisson regression of log deaths on linear PM variables; but they employed Bayesian model averaging to consider a wide variety of variations in the basic model. They considered three regions: the Phoenix metropolitan area; a small subset of zip code to give a region presumably with uniform $PM_{2.5}$; and a still smaller zip code region surrounding the monitoring site (thought to be uniform as to PM_{10} concentrations). The models considered lags of 0, 1, 2, or 3 days but only for single day PM variables (no running

averages as used by Smith et al., 2000). A PM effect with a reasonable probability was found only in the uniform $PM_{2.5}$ region and only for coarse PM.

Mar et al. (2000, 2003) used conventional Poisson regression methods and limited their analyses to the smallest area (called "Uniform PM_{10}" by Clyde et al., 2000). They reported modeling data for lag days 0 to 4. Coarse fraction PM was marginally significant on lag day 0. No direct fine particle measures were statistically significant on day 0. A regional sulfate factor determined from source apportionment, however, was statistically significant. No correlations were reported for the source apportionment factors, but the correlation coefficient between sulfur (S) in $PM_{2.5}$ (as measured by XRF) with coarse fraction PM was only 0.13, suggesting separate and distinct effects for regional sulfate and coarse fraction PM.

The above three studies of PM- total mortality relationships in Phoenix tend to suggest a statistical association of coarse fraction PM with total elderly mortality in addition to and different from any relationship with fine PM, fine PM components, or source factors for fine PM.

With regard to long-term PM exposure effects on total (non-accidental) mortality, the newly available evidence from the HEI Reanalyses of Harvard Six Cities and ACS data (and extensions, thereof), substantiate well associations attributable to chronic exposures to inhalable thoracic particles (indexed by PM_{15} or PM_{10}) and the fine fraction of such particles (indexed by $PM_{2.5}$ and/or sulfates). Statistically significant excess risk for total mortality was shown by the reanalyses to fall in the range of 4-18% per 20 $\mu g/m^3$ $PM_{15/10}$ increment and 14-28% per 10 $\mu g/m^3$ $PM_{2.5}$ increase.

Source-Oriented Analyses of Particle Component Contributions

Other recent studies on the relation of mortality to particle composition and source (Laden et al., 2000; Mar et al., 2000; Özkaynak et al., 1996; Tsai et al., 2000) suggest that particles from certain sources may have much higher potential for adverse health effects than others, as shown by source-oriented evaluations involving factor analyses. For example, Laden et al. (2000) conducted factor analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study data for 1979-1988. For all six cities combined, the excess risk for daily mortality was estimated to be 9.3% (95% CI; 4.0, 14.9) per 25 $\mu g/m^3$ $PM_{2.5}$ (average of 0 and 1 day lags) increment in a mobile source factor; 2.0% (95% CI; –0.3, 4.4) for a coal source factor, and –5.1% (95% CI;

–13.9, 4.6) for a crustal factor. There was large variation among the cities and suggestion of an association (not statistically significant) with a fuel oil factor identified by V or Mn.

Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995-1997 fine particle elemental components and gaseous pollutants (CO, NO_2, SO_2) in an area of Phoenix, AZ, close to the air pollution monitors. The $PM_{2.5}$ constituents included sulfur, Zn, Pb, soil-corrected potassium, organic and elemental carbon, and a soil component estimated from oxides of Al, Si, and Fe. Based on models fitted using one pollutant at a time, statistically significant associations were found between total mortality and PM_{10}, CO (lags 0 and 1), NO_2 (lags 0, 1, 3, 4), S (negative), and soil (negative). Statistically significant associations were also found between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4), $PM_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $PM_{10-2.5}$ (lag 0), and elemental, organic, or total carbon. Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2), and a regional sulfate factor (with a high loading on S). However, total mortality was negatively associated with a soil factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated with the regional sulfate factor.

Tsai et al. (2000) analyzed daily time-series of total and cardiorespiratory deaths, using short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to inhalable particle mass (PM_{15}) and fine particle mass ($PM_{2.5}$), the study evaluated data for metals (Pb, Mn, Fe, Cd, V, Ni, Zn, Cu) and for three fractions of extractable organic matter. Factor analyses were carried out using the metals, CO, and sulfates. The most significant sources or factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO, industrial Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and sulfates were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden oil burning and motor vehicle emissions predicted total mortality, but copper showed a marginal negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn showed marginal negative associations with mortality, as did industrial sources traced by Cu.

The set of results from the above factor analyses studies do not yet allow one to identify with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless, some commonalities across the studies seem to highlight the likely importance of mobile source and other fuel combustion emissions (and apparent lesser importance of crustal particles) as contributing to increased total or cardiorespiratory mortality.

8.4.4.1.2 Cause-Specific Mortality Effects

Cardiovascular- and Respiratory-Related Mortality

Numerous new studies have evaluated PM-related effects on cause-specific mortality. Most all report positive, often statistically significant (at $p < 0.05$), short-term (24-h) PM exposure associations with CVD- and respiratory-related deaths. Cause-specific 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 cardiovascular or combined cardiorespiratory 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. Effect size estimates for the coarse fraction ($PM_{10-2.5}$) for cause-specific mortality generally fall in the range of ca. 3.0 to 8.0% for cardiovascular and ca. 3.0 to 16.0% for respiratory causes per 25 $\mu g/m^3$ increase in $PM_{10-2.5}$.

Also of particular interest, the above noted study by Mar et al. examined the associations of a variety of PM indicators with cardiovascular mortality (for age $\geq$65), again in the zip code area near the Phoenix monitoring site. For this end point, coarse PM was statistically significant on lag day 0 but not on subsequent lag days. $PM_{2.5}$ and a number of fine PM indicators were statistically significant on lag day 1 but not on lag day 0. This suggests a distinct and separate relationship of $PM_{2.5}$ and $PM_{10-2.5}$. As in the case of total mortality, the only fine PM indicator found to be statistically significant on lag day 0 was regional sulfate. However, the low correlation coefficient between S in $PM_{2.5}$ and $PM_{10-2.5}$ ($r = 0.13$) suggests that the two relationships represent different sets of deaths. Thus, there is some evidence suggesting that the risk of cardiovascular mortality, as well as that of total mortality, may be statistically associated with $PM_{10-2.5}$ – possibly independent of any relationships with fine particle indicators.

Long-Term PM Exposure and Lung Cancer

Of particular interest with regard to PM-related cause-specific mortality is growing evidence linking long-term PM exposure with increased risk of lung cancer. Historical evidence

includes studies of lung cancer trends, studies of occupational groups, comparisons of urban and rural populations, and case-control and cohort studies using diverse exposure metrics (Cohen and Pope, 1995). Numerous past ecological and case-control studies of PM and lung cancer have generally indicated a lung cancer RR greater than 1.0 to be associated with living in areas having higher PM exposures despite possible problems with respect to potential exposure and other risk factor measurement errors. Table 8-37 provides a partial listing of such studies.

TABLE 8-37. SUMMARY OF PAST ECOLOGIC AND CASE-CONTROL EPIDEMIOLOGIC STUDIES OF OUTDOOR AIR AND LUNG CANCER

Study Type	Authors	Locale	Exposure Classification	Rate Ratio (95% CI)
Ecologic	Henderson et al., 1975	Los Angeles, CA	High PAH Areas	1.3 @ 96-116 ug/m^3 TSP (CI: N/A)
	Buffler et al., 1988	Houston, TX	TSP by Census Tract	1.9 @ 16 ug/m^3 TSP (CI: N/A)
	Archer, 1990	Utah	TSP by county	1.6 @ 85 ug/m^3 TSP (CI: N/A)
Case-Control	Pike et al., 1979	Los Angeles	BAP Geo. Areas	1.3 @ 96-116 ug/m^3 TSP
	Vena, 1982	Buffalo, NY	TSP Geo. Areas	1.7 @ 80-200 ug/m^3 TSP (CI: 1.0-2.9)
	Jedrychowski, et al., 1990	Cracow, Poland	TSP and SO_2 Geo. Areas	1.1 @ TSP > 150 ug/m^3 (CI: N/A)
	Katsouyanni, et al., 1990	Athens, Greece	Soot Concentration Geo. Areas	1.1 @ soot up to 400 ug/m^3 (CI: N/A)
	Barbone et al., 1995	Trieste, Italy	High Particle Deposition Areas	1.4 @ > 0.3 g/m^2/day (CI: 1.1-1.8)
	Nyberg et al., 2000	Stockholm, Sweden	High NO_2 Areas	1.3 (CI: 0.9-1.9)

Source: Derived from Cohen (2000).

Prospective cohort studies offer a potentially more powerful approach to evaluation of apparent associations between PM exposures and development of lung cancer. The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) summarized three of these more elaborate studies that carefully evaluated PM air pollution exposure effects on lung cancer using

the prospective cohort design. In the AHSMOG Study, Abbey et al. (1991) followed a cohort of Seventh Day Adventists, whose extremely low prevalence of smoking and uniform, relatively healthy dietary patterns reduce the potential for confounding by these factors. Excess lung cancer incidence was observed in females in relation to both particle (TSP) and O_3 exposure after 6 years follow-up time. Dockery et al. (1993) reported the results of a 14- to 16-year prospective follow-up of 8,111 adults living in six U.S. cities that evaluated associations between air pollution and mortality. After controlling for individual differences in age, sex, cigarette smoking, BMI, education, and occupational exposure, Dockery et al. (1993) found an elevated but non-significant risk for lung cancer (RR = 1.37; 95% CI = 0.81 to 2.31) for a difference in $PM_{2.5}$ pollution equal to that of the most polluted versus the least polluted city. Pope et al. (1995) similarly analyzed $PM_{2.5}$ and sulfate ($SO_4^=$) air pollution as predictors of mortality in a prospective study of 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS).

Both the ACS and Harvard studies have been subjected to much scrutiny, including an extensive independent audit and reanalysis of the original data (Krewski et al., 2000) that confirmed the originally published results. The ACS study controlled for individual differences in age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education, BMI, and alcohol use. Lung cancer mortality was significantly associated with particulate air pollution when $SO_4^=$ was used as the index,, but not when $PM_{2.5}$ mass was used as the index for a smaller subset of the study population that resided in metropolitan areas where $PM_{2.5}$ data were available from the Inhalable Particle (IP) Network. Thus, while these prospective cohort studies have also indicated that long-term PM exposure is associated with an increased cancer risk, the effect estimates were generally not statistically significant, quite possibly due to inadequate statistical power by these studies at that time (e.g., due to inadequate population size and/or follow-up time for long-latency cancers).

The AHSMOG investigators have re-examined the association between long-term PM exposure and increased risk of both lung cancer incidence and lung cancer mortality in nonsmokers using longer-term follow-up of this cohort and improved analytical approaches. Beeson et al. (1998) considered this cohort of some 6,338 nonsmoking, non-Hispanic, white Californian adults, ages 27-95, that was followed from 1977 to 1992 for newly diagnosed cancers. Incident lung cancer in males was positively and significantly associated with

interquartile range (IQR) increases for mean concentrations of PM_{10} (RR = 5.21; 95% CI = 1.94-13.99). For females in the cohort, incident lung cancer was positively associated with IQR increases for SO_2 (RR = 2.14; CI, 1.36-3.37) and IQR increases for PM_{10} exceedance frequencies of 50 $\mu g/m^3$ (RR = 1.21; 95% CI = 0.55-2.66) and 60 ug/m^3 (RR = 1.25; 95% CI = 0.57-2.71). Thus, increased risks of incident lung cancer were deemed by the authors to be associated with elevated long-term ambient concentrations of PM_{10} and SO_2 in both genders. The higher PM_{10} risk effect estimate for cancer in males appeared to be partially due to gender differences in long-term air pollution exposures. Abbey et al. (1999) also related long-term ambient concentrations of PM_{10}, SO_4^{-2}, SO_2, O_3, and NO_2 to 1977-1992 mortality in the AHSMOG cohort. After adjusting for a wide array of potentially confounding factors, including occupational and indoor sources of air pollutants, PM_{10} showed a strong association with lung cancer deaths in males (PM_{10} IQR RR=2.38; 95% CI: 1.42 - 3.97). In this cohort, males spent more time outdoors than females, thus having higher estimated air pollution exposures than the cohort females. Ozone showed an even stronger association with lung cancer mortality for males, and SO_2 showed strong associations with lung cancer mortality for both sexes. The authors reported that other pollutants showed weak or no association with mortality. Therefore, increases in both lung cancer incidence and lung cancer mortality in the extended follow-up analysis of the AHSMOG study were found to be most consistently associated with elevated long-term ambient concentrations of PM_{10} and SO_2, especially among males.

A recent follow-up analysis of the major ACS study by Pope et al. (2002) responds to a number of criticisms previously noted for the earlier ACS analysis (Pope et al., 1995) in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Most notably, the new study examined other pollutants, had better occupational indices and diet information, and also addressed possible spatial auto-correlations due to regional location. The recent extension of the ACS study included ~500,000 adult men and women drawn from ACS-CPS-II enrollment and follow-up during 1982-1998. This new analysis of the ACS cohort substantially expands the prior analysis, including: (1) more than doubling of the follow-up time to 16 years (and more than tripling of the number of deaths in the analysis); (2) substantially expanded exposure data, including gaseous co-pollutant data and new $PM_{2.5}$ data collected in 1999-2001; (3) improved control of occupational exposures; (4) incorporation of dietary variables that account for total fat consumption, as well as that of vegetables, citrus and high-fiber grains; and (5) utilization of

recent advances in statistical modeling, including incorporation of random effects and non-parametric spatial smoothing components in the Cox proportional hazards model.

In the extended ACS analysis, long-term exposure to air pollution, and especially to $PM_{2.5}$, was found to be associated with increased annual risk of mortality. With the longer 15-year follow-up period and improved $PM_{2.5}$ exposure metrics, this study detected for the first time, a statistically significant association between living in a city with higher $PM_{2.5}$ and increased risk of dying of lung cancer. Each 10 ug/m^3 increment in annual average fine PM was associated with a 13 percent (95% CI=4%-23%) increase in lung cancer mortality. Coarse particles and gaseous pollutants were generally not significantly associated with excess lung cancer mortality. SO_4^{-2} was significantly associated with mortality and lung cancer deaths in this extended data set, yielding RR's consistent with (i.e., not significantly different from) the SO_4^{-2} RR's reported in the previously published 7-year follow-up (Pope et al, 1995). However, while $PM_{2.5}$ was specific to the causes most biologically plausible to be influenced by air pollution in this analysis (i.e., cardiopulmonary and cancer), SO_4^{-2} was significantly associated with every mortality category in this new analysis, including that for "all-other causes". This suggests that the $PM_{2.5}$ associations found are more biologically plausible than the less specific SO_4^{-2} associations found. The $PM_{2.5}$ cancer risk appears greatest for non-smokers and among those with lower socio-economic status (as indicated by lower educational attainment).

Overall, these new cohort studies confirm and strengthen the published older ecological and case-control evidence indicating that living in an area that has experienced higher PM exposures can cause a significant increase in the RR of lung cancer incidence and associated mortality. In particular, the new ACS cohort analysis more clearly indicates that living in a city with higher $PM_{2.5}$ levels is associated with an elevated risk of lung cancer amounting to an increase of some 10 to 15% above the lung cancer risk in a cleaner city.

With regard to specific ambient fine particle constituents that may significantly contribute to the observed ambient PM-related increases in lung cancer, PM components of diesel engine exhaust represent one class of likely important contributors. Diesel emission PM typically comprises a noticeable fraction of ambient fine particles in many urban areas, having been estimated to comprise from approximately 5 to 35% of ambient $PM_{2.5}$ in some U.S. urban areas (see Chapter 3). In addition, as discussed in a separate Health Effects Assessment of Diesel Engine Exhaust (U.S. Environmental Protection Agency, 2002), extensive epidemiologic and

toxicologic evidence links diesel emissions (including fine PM components) to increased risk of lung cancer.

8.4.4.2 PM_{10}, $PM_{2.5}$ (Fine), and $PM_{10-2.5}$ (Coarse) Particulate Matter Effects on Morbidity

A body of new studies published since the 1996 PM AQCD provides further evidence examining ambient PM association with increased human morbidity. At the time of the 1996 PM AQCD, fine particle morbidity studies were mostly limited to Schwartz et al. (1994) , Neas et al. (1994, 1995); Koenig et al. (1993); Dockery et al. (1996); and Raizenne et al. (1996); and discussion of coarse particles morbidity effects was also limited to only a few studies (Gordian et al., 1996; Hefflin et al., 1994). Since the 1996 PM AQCD, several new studies have been published in which newly available size-fractionated PM data allowed investigation of the effects of both fine ($PM_{2.5}$) and coarse fraction ($PM_{10-2.5}$) particles. PM_{10}, fine (FP) and coarse fraction (CP) particle results are noted below for studies by morbidity outcome areas, as follows: cardiovascular disease (CVD) hospital admissions (HA's); respiratory medical visits and hospital admissions; and respiratory symptoms and pulmonary function changes.

As discussed in Section 8.3.1 (on cardiovascular effects associated with acute ambient PM exposure), a substantial body of new results has emerged since the 1996 PM AQCD that evaluates PM_{10} effects on cardiovascular-related hospital admissions and visits. Especially notable new evidence has been provided by multi-city studies (Samet et al., 2000a,b; Zanobetti and Schwartz, 2003b) that yield pooled estimates of PM-CVD effects across numerous U.S. cities and regions. This study found not only significant PM associations, but also associations with other gaseous pollutants as well, thus hinting at likely independent effects of certain gases (O_3, CO, NO_2, SO_2) and/or interactive effects with PM. These and other individual-city studies generally appear to confirm likely excess risk of CVD-related hospital admission for U.S. cities in the range of 2-9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 yr).

In addition to the PM_{10} studies, several new U.S. and Canadian studies evaluated fine-mode PM effects on cardiovascular outcomes. Lippmann et al. (2000) and Ito (2003) report a positive but not a significant association with $PM_{2.5}$; and Moolgavkar (2003) reported $PM_{2.5}$ to be significantly associated with CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997a) reported that fine particles were significantly associated with CVD HA in a single pollutant model, but not when gases were included in multipollutant models for the 8 largest Canadian

city data. Stieb et al. (2000) reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED) visits in single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported that $PM_{2.5}$ measured by nepholonetry was associated with CVD HA for all ages and 65+ yr, but not in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao et al., 1999; Creason et al., 2001; Pope et al., 1999b,c) reported associations between increases in $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (2000) reported a negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate variability measure). A study by Peters and colleagues (2001a) reported significant temporal associations between acute (2-h or 24-h) measures of $PM_{2.5}$ and myocardial infarction. Overall, these new studies collectively appear to implicate fine particles, as well as possibly some gaseous co-pollutants, in cardiovascular morbidity, but the relative contributions of fine particles acting alone or in combination with gases such as O_3, CO, NO_2 or SO_2 remain to be more clearly delineated and quantified. The most difficult issue relates to interpretation of reduced PM effect size and /or statistical significance when co-pollutants derived from the same source(s) as PM are included in multipollutant models.

Section 8.3.1 also discussed U.S. and Canadian studies that present analyses of coarse fraction particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) and Ito (2003) found significant positive associations of $PM_{10-2.5}$ with ischemic heart disease hospital admissions in Detroit (RR = 1.08, CI 1.04, 1.16). Tolbert et al. (2000a) reported significant positive associations of heart dysrhythmias with CP ($p = 0.04$) as well as for elemental carbon ($p = 0.004$), but these preliminary results must be interpreted with caution until more complete analyses are carried out and reported. Burnett et al. (1997b) noted that CP was the most robust of the particle metrics examined to inclusion of gaseous covariates for cardiovascular hospitalization, but concluded that particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory disease in this study. Based on another Canadian study, Burnett et al. (1999), reported statistically significant associations for CP in univariate models but not in multipollutant models; but the use of estimated rather than measured PM exposures indices limits the interpretation of the PM results reported.

The collective evidence reviewed above, in general, appears to suggest excess risks for CVD-related hospital admissions of approximately 1 to 10% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ increment.

Section 8.3.2 also discussed new studies of effects of short-term PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ exposure on the incidence of respiratory hospital admissions and medical visits. Several new U.S. and Canadian studies have yielded particularly interesting results that are also suggestive of roles of both fine and coarse particles in respiratory-related hospital admissions. In an analysis of Detroit data, Lippmann et al. (2000) and Ito (2003) found comparable effect size estimates for $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess risk for pneumonia hospital admissions (in no co-pollutant model) was 18.6% (CI 5.6, 33.1) per 50 $\mu g/m^3$ PM_{10}, 10% (CI 1.5, 19.5) per 25 $\mu g/m^3$ $PM_{2.5}$ and 11.2% (CI -0.02, 23.6) per 25 $\mu g/m^3$ $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not highly correlated, the observed association between coarse particles and health outcomes were possibly not confounded by smaller particles. Despite the greater measurement error associated with $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10}, this indicator of the coarse particles within the thoracic fraction was associated with some of the outcome measures. The interesting result is that $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics. Burnett et al. (1997b) also reported PM (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) associations with respiratory hospital admissions, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was significant (RR = 1.13 for 25 $\mu g/m^3$; CI = 1.05 - 1.20); and inclusion of ozone still yielded a significant coarse mass RR = 1.11 (CI = 1.04 – 1.19). Moolgavkar (2000a) and Moolgavkar (2003) reported that, in Los Angeles, both PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different lags for single pollutant models but not in two pollutant models. Delfino et al. (1997) reported that both $PM_{2.5}$ and PM_{10} are positively associated with ED visits for respiratory disease. Morgan et al. (1998) reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$ association with COPD hospital admissions for 1-hr max PM that was more positive than 24-h average $PM_{2.5}$.

A new study examines PM associations with asthma-related hospital admissions. Sheppard et al. (1999) and Sheppard (2003) studied relationships between PM metrics that included $PM_{10-2.5}$ and non-elderly adult hospital admissions for asthma in the greater Seattle area and reported significant relative risks for PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10-2.5}$, the relative risk was 1.05 (95% CI 1.0, 1.14) and for PM2.5, the relative risk 1.07 (1.02, 1.11).

For a 16% decrease in PM_{10} levels, Friedman et al. (2001) reported decreased hospital admissions for asthmatics during the Olympics in Atlanta.

Thus, although PM_{10} mass has most often been implicated as the PM pollution index affecting respiratory hospital admissions, the overall collection of new studies reviewed in Section 8.3.2 appear to suggest relative roles for PM_{10} and for both fine and coarse PM mass fractions, such as $PM_{2.5}$ and $PM_{10-2.5}$.

Section 8.3.3 assessed relationships between PM exposure on lung function and respiratory symptoms. While most data examine PM_{10} effects, several studies also examined fine and coarse fraction particle effects. Schwartz and Neas (2000) report that cough was the only response in which coarse fraction particles appeared to provide an independent contribution to explaining the increased incidence. The correlation between CP and $PM_{2.5}$ was moderate (0.41). Coarse fraction particles had little association with evening peak flow. Tiittanen et al. (1999) also reported a significant effect of $PM_{10-2.5}$ for cough. Thus, cough may be an appropriate outcome related to coarse fraction particle effects. However, the limited data base suggests that further study is appropriate. The report by Zhang, et al. (2000) of an association between coarse fraction particles and the indicator "runny nose" is noted also.

Published epidemiologic studies have collectively indicated that exposure to PM air pollution can be associated with adverse human health effects, and that asthmatics represent a population that can be especially affected by acute exposures to air pollution (e.g., see Koren and Utell, 1997). In particular, prospective epidemiologic studies of panels of individuals confirm the air pollution-asthma exacerbation association.

For respiratory symptoms and PFT changes, several new asthma studies report associations with ambient PM measures. The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Pekkanen et al. (1997) and Romieu et al. (1996) found comparable results for $PM_{2.5}$ and PM_{10} and the study of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$. Of studies that included both PM_{10} and $PM_{2.5}$ in their analyses of respiratory symptoms, the studies of Peters et al. (1997c) and found similar effects for the two PM measures. Only the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$. While the PM associations with adverse health effects among asthmatics and others are well documented, the type/source(s) of those particles most associated with adverse health effects among

asthmatics are not known at this time. Indeed, the makeup of PM varies greatly from place to place and over time, depending upon factors such as the sources that contribute to the pollution and the prevailing atmospheric conditions, affecting particle formation, coagulation, transformation, and transport. One suspected causal PM agent is the fine particle component of diesel combustion exhaust.

Two studies (Delfino et al., 1998; Ostro et al., 2001) examined PM effects on asthmatics using one hour maximum exposure measures by TEOM, and both studies indicate a relationship with measures of respiratory symptoms. Further research is needed at these shorter exposure times for different PM size fractions.

For non-asthmatics, several studies evaluated $PM_{2.5}$ effects. Naeher et al. (1999) reported similar AM PEF decrements for both $PM_{2.5}$ and PM_{10}. Neas et al. (1996) reported a nonsignificant negative association for PEF and $PM_{2.1}$, and Neas et al. (1999) also reported negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significantly PM PEF association with $PM_{2.5}$, and Tiittanen et al. (1999) also reported negative but nonsignificant association for PEF and $PM_{2.5}$. Gold et al. (1999) reported significantly PEF results. Schwartz and Neas (2000) reported significant $PM_{2.5}$ effects relative to lower respiratory symptoms. Tiittanen et al. (1999) showed significant effects for cough and $PM_{2.5}$ for a 4-day average.

The best evidence for chronic effects are found in the newer studies that combine the features of cross-sectional and cohort studies. These studies include Peters et al. (1999b,c), Gauderman et al. (2000), and Gauderman et al. (2002). The Gauderman studies found significant decreases in lung function growth related to PM_{10} levels. However, Peters et al. (1999) found no relationship between symptoms and PM_{10} levels. The cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), reported in the previous 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle acidity.

The above new studies offer much more information than was available in 1996. Effects were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory hospital admissions and cough. Still insufficient data exists from these relatively limited studies to allow strong conclusions at this time as to which size-related ambient PM components may be most strongly related to one or another morbidity endpoints. Very preliminarily, however, fine particles appear to be more strongly implicated in cardiovascular outcomes than are coarse fraction particles, whereas both seem to impact respiratory endpoints.

8.4.5 The Question of Lags

The effect of selecting lags on the resulting model for PM health effects is an important issue in model selection. Using simulated data with parameters similar to a Seattle $PM_{10-2.5}$ data series, Lumley and Sheppard (2000) showed that the bias resulting from the selection is shown to be similar in size to the relative risk estimates from the measured data. More precisely, the log relative risk from the measured Seattle data is about twice the mean bias in the simulated control data, and the published estimate of relative risk is only at the 90^{th} percentile of the bias distribution in these control analysis. The selection rule used was to choose the lag (between 0 and 6 day) with the largest estimated relative risk. In comparisons to real data from Seattle for other years and from Portland, OR (with similar weather patterns to Seattle), similar bias issues became evident.

In most of the past air pollution health effects time-series studies, after the basic model (the best model with weather and seasonal cycles as covariates) was developed, several pollution lags (usually 0 to 3 or 4 days) were individually introduced and the most significant lag(s) chosen for the RR calculation. While this practice may bias the chance of finding a significant association, without a firm biological reason to establish a fixed pre-determined lag, it appears reasonable. Due to likely individual variability in response to air pollution, the apparent lags of effects observed for aggregated population counts are expected to be "distributed" (i.e., symmetric or skewed bell-shape). The "most significant lag" in such distributed lags is also expected to fluctuate statistically. The "vote-counting" of the most significant lags reported in the past PM-mortality studies shows that 0 and 1 day lags are, in that order, the most frequently reported "optimal" lags, but such estimates may be biased because these lags are also likely the most frequently examined ones. Thus, a more systematic approach across different data sets was needed to investigate this issue.

The Samet et al. (2000b) analysis, and the reanalysis by Dominici et al. (2002), of the 90 largest U.S. cities provides particularly useful information on this matter. Figure 8-19 depicts the Dominici et al. (2002) overall pooled results, showing the posterior distribution of PM_{10} effects for the 90 cities for lag 0, 1, and 2 days. It can be seen that the effect size estimate for lag 1day is about twice that for lag 0 or lag 2 days, although their distributions overlap. The pattern of lagged effects pooled for each of the seven regions (see Figure 8-5) in the 90 cities study also shows that the lag with the largest effect was at 1 day, with the exception of Upper Midwest

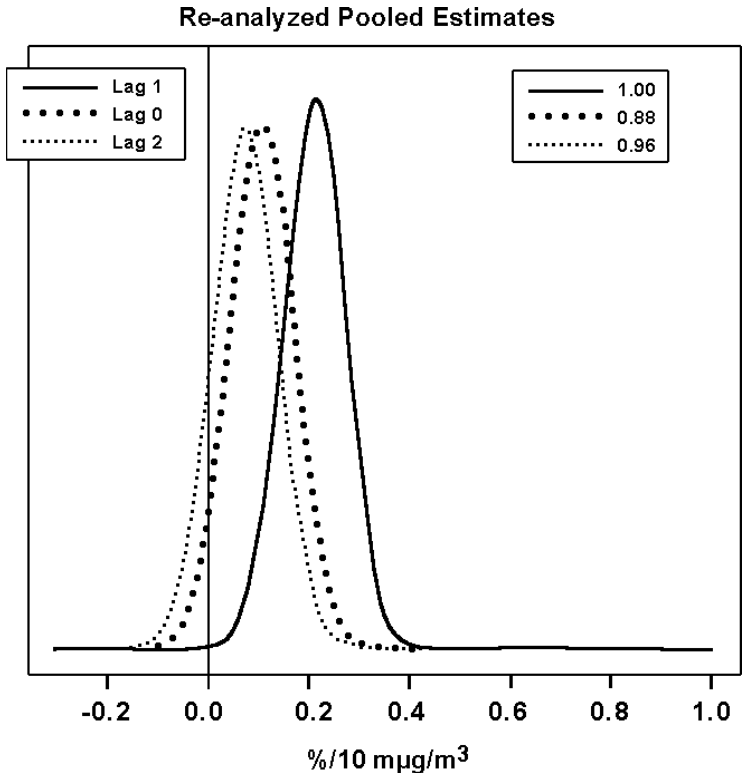

Figure 8-19. Marginal posterior distribution for effects of PM_{10} on all cause mortality at lag 0, 1, and 2 for the 90 cities. From Dominici et al. (2002a). The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

Source: Dominici et al. (2002).

where the estimated PM_{10} effect was about the same for lag 0 and 1 days. However, the studies that examined PM-mortality associations in individual cities sometimes show the "most significant lags" at other lags. For example, in Moolgavkar's analysis of Los Angeles data (2000 and reanalysis 2003), both total non-accidental mortality and cardiovascular mortality showed the strongest associations with PM_{10} at lag 2 days.

A review of current studies on the short-term adverse health effects of air pollution indicates that there are essentially three different approaches to deal with temporal structure: (1) assume all sites have the same lag (e.g., 1 day, for a given effect); (2) use the lag or moving average giving the largest or most significant effect and for each pollutant and endpoint; and

(3) use a flexible distributed lag model, with parameters adjusted to each site. The NMMAPS mortality analyses used the first approach. This approach introduces a consistent response model across all locations. However, since the cardiovascular, respiratory, or other causes of acute mortality usually associated with PM are not at all specific, there is little *a priori* reason to believe that they must have the same relation to current or previous PM exposures at different sites. The obvious advantage of the first approach in dealing with multi-city data is its consistency in summarizing the point estimate. The major factor that makes it difficult to conduct a meta-analysis of existing PM health effects studies is the lack of consistency in the way lag structures were modeled across the studies.

The approach used in most of PM time-series studies is to use the model that maximizes some global model goodness-of-fit criterion. This leads to selection of different models at different sites, as might be expected. However, the best-fitting model (for lags, for example) is often the model with the largest or most significant PM_{10} coefficient (i.e., the approach [2] above). All models for the pollutant(s) of interest are usually compared among themselves only after a preliminary baseline model has been fitted. The baseline model takes into account most of the other variables with which PM_{10} could be plausibly associated, so that the remaining variation in morbidity or mortality that can be explained by including PM_{10} indicators with different temporal structures is nearly "orthogonal" or independent of the baseline model. The restriction to the same lag day at all sites certainly increases the precision of that estimate, but possibly at the cost of obscuring different relationships between time of exposure and health effect at other sites.

An additional complication in assessing the shape of a distributed lag is that the apparent spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city and from pollutant to pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and may tend to obscure important nuances of lag structures that may provide important clues to possible different lags between PM exposures and different cause-specific effects.

It should also be noted that if one chooses the most significant single lag day only, and if more than one lag day shows positive (significant or otherwise) associations with mortality, then reporting a RR for only one lag would also underestimate the pollution effects. Schwartz (2000b; reanalysis 2003b) investigated this issue, using the 10 U.S. cities data where daily PM_{10}

values were available for 1986-1993. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model (with stringent convergence criteria) and penalized splines adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were fitted. Effects of distributed lag were examined using two models: second-degree distributed lag model using lags 0 through 5 days; and unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results. The results indicated that the effect size estimates for the quadratic distributed model and unconstrained distributed lag model using GAM were similar: 6.3% (95% CI: 4.9-7.8) per 50 $\mu g/m^3$ increase for the quadratic distributed lag model, and 5.8% (95% CI: 4.4-7.3). These risk estimates are about twice as large as the two-day average (lag 0 and 1 day) estimate (3.4%; 95% CI: 2.6-4.1) obtained in the reanalysis of the original 10 cities study (Schwartz, 2003b). There are indications that such distributed lag estimates are even larger when more specific cause of deaths are examined (see US 10 cities study description in section 8.2.2.3).

Mis-specification of the lag structure may cause important modeling biases. Most of the published literature for the U.S. evaluates only single-day models, a choice dictated by the every-sixth-day sampling schedule used for PM_{10} in many U.S. cities. When this occurs, it is not possible to evaluate multi-day models with greater biological plausibility, such as moving average models and distributed lag models. It should also be noted that, with the every-sixth-day PM data, a different set of days of mortality series were evaluated at each lag. An every-other-day sampling schedule was used in the Harvard Six City Study, for which the PM data on a given day has been used as though it were a two-day moving, alternately concurrent with mortality on half the days and lagging mortality by one day on the other days. While the most commonly used lags in PM time-series models are zero or one day, some studies have found PM effects with longer lags (e.g., Wichmann et al. (2000) and reanalysis by Stölzel et al. (2003); Lippmann et al. (2000) and reanalysis by Ito (2003). It is plausible that mortality or hospital admissions from PM may arise from different responses or PM-associated diseases with different characteristic lags, for example, that cardiovascular responses may arise almost immediately after exposure, within zero or one days or even within two hours (Peter et al., 2001a, for myocardial infarction). One would then expect to see different best-fitting lags for different cause-specific mortality or hospital admissions.

In summary, the largest time-series study to date (90 cities study) indicated that, of the 0, 1, and 2 day PM_{10} lags examined, lag 1 day showed the strongest mortality associations. However, other lags are reported for various mortality and morbidity outcomes from studies that examined individual cities' data. Examinations of lag structures are often limited by the prevailing every-6th-day sampling schedule for PM in the U.S., but a limited number of studies that examined daily PM data using distributed lag model suggest that multi-day effects are larger than the single-day effects. Thus, it is possible that current PM risk estimates, most frequently computed for a single day or for two-day averages, may be underestimating these multi-day effects.

8.4.6 Concentration-Response Relationships for Ambient PM

In the 1996 PM AQCD, the limitations of identifying 'threshold' in the concentration-response relationships in observational studies were discussed including the low data density in the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Also, a threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that need to be noted. For example, Schwartz (1999) discussed that, since individual thresholds would vary from person to person due to individual differences in genetic level susceptibility and pre-existing disease conditions, it would be almost mathematically impossible for a threshold to exist in the population. This argument holds only if the most sensitive members of a population are sensitive to very low concentrations, which may not be the case. The person-to-person difference in the relationship between personal exposure and the concentration observed at a monitor would also add to the variability. Because one cannot directly measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed threshold, if any, biologically. Despite these issues, several studies have attempted to address the question of threshold by analyzing large databases, or by conducting simulations.

Daniels et al. (2000; reanalysis by Dominici et al., 2003) examined the presence of threshold using the largest 20 U.S. cities for 1987-1994. In the original analysis, the authors compared three log-linear GAM regression models: (1) using a linear PM_{10} term; (2) using a natural cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. The covariates included in these

models are similar to those used by the same research group previously (Kelsall et al., 1997; Samet et al., 2000a,b), including the smoothing function of time, temperature and dewpoint, and day-of-week indicators. In the reanalysis, the covariate adjustments were made using natural splines in GLM models. Total, cardiorespiratory, and other mortality series were analyzed. These models were fit for each city separately, and for model (1) and (2) the combined estimates across cities were obtained by using inverse variance weighting if there was no heterogeneity across cities, or by using a two-level hierarchical model if there was heterogeneity. The best fit among the models, within each city and over all cities, were also determined using the Akaike's Information Criterion (AIC). The results using the natural spline model showed that, for total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold (see Figure 8-20). For mortality from other causes, however, the curve did not increase until PM_{10} concentrations exceeded 50 $\mu g/m^3$. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models. Thus, these results suggest that linear models without a threshold may well be appropriate for estimating the effects of PM_{10} on the types of mortality of main interest.

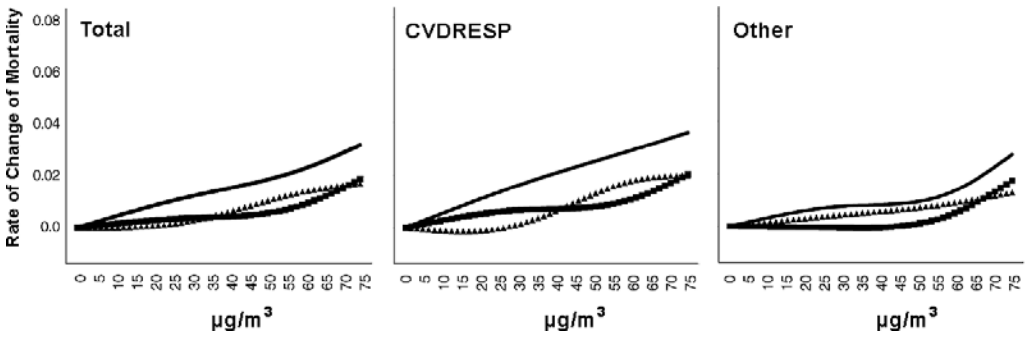

Figure 8-20. Particulate matter < 10 μm in aerodynamic diameter (PM_{10})-total mortality concentration-response curves for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (OTHERS) mortality, 20 largest US cities, 1987-1994. The concentration-response curves for the mean lag, current day, and previous day PM_{10} are denoted by solid lines, squared points, and triangle points, respectively.

Source: Dominici et al. (2003).

Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time-series studies. Based on the realistic range of error observed from actual Toronto pollution data (average site-to-site correlation: 0.90 for O_3; 0.76 for CoH; 0.69 for TSP; 0.59 for SO_2; 0.58 for NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were generated with three PM_{10} threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$). LOESS with a 60% span was used to observe the exposure-response curves for these 18 combinations of exposure-response relationships with error. A parameter threshold model was also fit using non-linear least squares. Both mortality and PM_{10} data were pre-filtered for the influence of seasonal cycles using LOESS smooth function. The threshold regression models were then fit to the pre-filtered data. Graphical presentations indicate that LOESS adequately detects threshold under no error, but the thresholds were "smoothed out" under the extreme error scenario. Use of a parametric threshold model was adequate to give "nearly unbiased" estimates of threshold concentrations even under the conditions of extreme measurement error, but the uncertainty in the threshold estimates increased with the degree of error. They concluded, "if threshold exists, it is highly likely that standard statistical analysis can detect it."

The Smith et al. (2000) study of associations between daily total mortality and $PM_{2.5}$ and $PM_{10-2.5}$ in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold. In the linear model, the authors found that mortality was significantly associated with $PM_{10-2.5}$, but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model in which several possible thresholds were specified; and (2) a B-spline (spline with cubic polynomials) model with 4 knots. Using the piecewise model, there was no indication that there was a threshold for $PM_{10-2.5}$ However, for $PM_{2.5}$, the piecewise model resulted in suggestive evidence for a threshold, around 20 to 25 $\mu g/m^3$. The B-spline results also showed no evidence of threshold for $PM_{10-2.5}$, but for $PM_{2.5}$, a non-linear curve showed a change in the slope around 20 $\mu g/m^3$. A further Bayesian analysis for threshold selection suggested a clear peak in the posterior density of $PM_{2.5}$ effects around 22 $\mu g/m^3$. These results, if they in fact reflect reality, make it difficult to evaluate the relative roles of different PM components (in this case, $PM_{2.5}$ versus $PM_{10-2.5}$). However, the concentration-response curve for $PM_{2.5}$ presented in this publication suggests more of a U- or V-shaped relationship than the usual "hockey stick" relationship. Such a relationship is, unlike the temperature-mortality relationship, difficult to

interpret biologically. Because the sample size of this data (3 years) is relatively small, further investigation of this issue using similar methods but a larger data set is warranted. Other studies evaluate non-linear relationships using a multi-city meta-smoothing approach based on non- or semi-parametric smoothers rather than on linear parametric models.

Smith et al. (1999) analyzed PM_{10}-mortality association in Birmingham, AL and Cook County, IL. Temperature was modeled using piece-wise linear term with a change point. PM_{10} were modeled at lag 0 through 3 and 3-day averages at these lags. In addition to the linear model, they also investigated the existence of a threshold using B-splines and a parametric threshold model with the profile log likelihood evaluated at changing threshold points. B-splines results suggest that an increasing effect above 80μg/m^3 for Birmingham, and above 100 μg/m^3 for Chicago. The threshold model through examination of log likelihood across the range of threshold levels also suggested similar change points, but not to the extent that could achieve statistical distinctions.

In summary, the results from large multi-city studies suggest that there is no strong evidence for a threshold mortality effect of PM. Some single city studies suggest a hint of a threshold, but not in a statistically clear manner. More data may need to be examined with alternative approaches (e.g., Smith et al.'s parametric model), but meanwhile, the use of linear PM effect model appears to be appropriate.

8.4.7 Heterogeneity of Particulate Matter Effects Estimates

Approximately 35 then-available acute PM exposure community epidemiologic studies were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality being associated with short-term (24-h) PM exposures indexed by various ambient PM measurement indices (e.g., PM_{10}, $PM_{2.5}$, BS, CoH, sulfates, etc.) in many different cities in the United States and internationally. Much homogeneity appeared to exist across various geographic locations, with many studies suggesting, for example, increased relative risk (RR) estimates for total nonaccidental mortality on the order of 1.025 to 1.05 (or 2.5 to 5.0% excess deaths) per 50 μg/m^3 increase in 24-h PM_{10}, with statistically significant results extending more broadly in the range of 1.5 to 8.0%. The elderly ≥ 65 yrs. old and those with preexisting cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City

Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to 1.056 (2.0 to 5.6% excess deaths) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.

Now, more than 80 new time-series PM-mortality studies assessed earlier in this chapter provide extensive additional evidence which, qualitatively, largely substantiates significant ambient PM-mortality relationships, again based on 24-h exposures indexed by a wide variety of PM metrics in many different cities of the United States, in Canada, in Mexico, and elsewhere (in South America, Europe, Asia, etc.). The newly available effect size estimates from such studies are reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996 PM AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increment in 24-h concentration; and new $PM_{2.5}$ excess estimates for short-term exposures generally fall in the range of 2 to 8% per 25 $\mu g/m^3$ increment in 24-h $PM_{2.5}$ concentration.

However, somewhat greater spatial heterogeneity appears to exist across newly reported study results, both with regard to PM-mortality and morbidity effects. The newly apparent heterogeneity of findings across locations is perhaps most notable in relation to reports based on multiple-city studies in which investigators used the same analytical strategies and models adjusted for the same or similar co-pollutants and meteorological conditions, raising the possibility of different findings reflecting real location-specific differences in exposure-response relationships rather than potential differences in models used, pollutants measured and included in the models, etc. Some examples of newly reported and well-conducted multiple-city studies include: the NMMAPS analyses of mortality and morbidity in 20 and 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2000a); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of eight largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S. counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several European cities (Katsouyanni et al., 1997; Zmirou et al., 1998). The recently completed large NMMAPS studies of morbidity and mortality in U.S. cities add especially useful and important information about potential U.S. within- and between-region heterogeneity.

HEI (2003a) concluded that after examining the NMMAPS GAM reanalyses by Dominici et al. (2002) that while formal tests of PM effects across cities did not indicate evidence of heterogeneity because of the individual-city effects standard error being generally large that the

power to assess the presence of heterogeneity was low and, as such, the possibility of heterogeneity still exists.

8.4.7.1 Evaluation of Heterogeneity of Particulate Matter Mortality Effect Estimates

In all of the U.S. multi-city analyses, the heterogeneity in the PM estimates across cities was not explained by city-specific characteristics in the 2nd stage model. The heterogeneity of effects estimates across cities in the multi-city analyses may be due to chance alone, to mis-specification of covariate effects in small cities, or to real differences from location to location in effects of different location-specific ambient PM mixes, for which no mechanistic explanations are yet known. Or, the apparent heterogeneity may simply reflect imprecise PM effect estimates derived from smaller-sized analyses of less extensive available air pollution data or numbers of deaths in some cities tending to obscure more precise effects estimates from larger-size analyses for other locations, which tend to be consistently more positive and statistically significant.

Some of these possibilities can be evaluated by using data from the NMMAPS study (Samet et al., 2000b). Data in Figure 8-3 for excess risk and 95% confidence intervals were plotted against the total number of effective observations, measured by the number of days of PM_{10} data times the mean number of daily deaths in the community. This provides a useful measure of the weight that might be assigned to the results, since the uncertainty of the RR estimate based on a Poisson mean is roughly inversely proportional to this product. That is, the expected pattern typically shows less spread of estimated excess risk with increasing death-days of data. A more refined weight index would also include the spread in the distribution of PM concentrations. The results are plotted in Figure 8-21 for all cities and Figure 8-22 for each of the 7 regions.

Figure 8-21 for all cities suggests some relationship between precision of the effects estimates and study weight, overall. That is, the more the mortality-days observations, the narrower the 95% confidence intervals and the more precise the effects estimates (with nearly all these for cities with $\geq$ log 9 mortality-days being positive and many statistically significant at $p \leq 0.05$).

The Figure 8-22 depiction for each of the 7 regions is also informative. In the Northeast, there is considerable homogeneity (not heterogeneity) of effect size for larger study-size cities, even with moderately wide confidence intervals for those with log mortality-days = 8 to 9, and

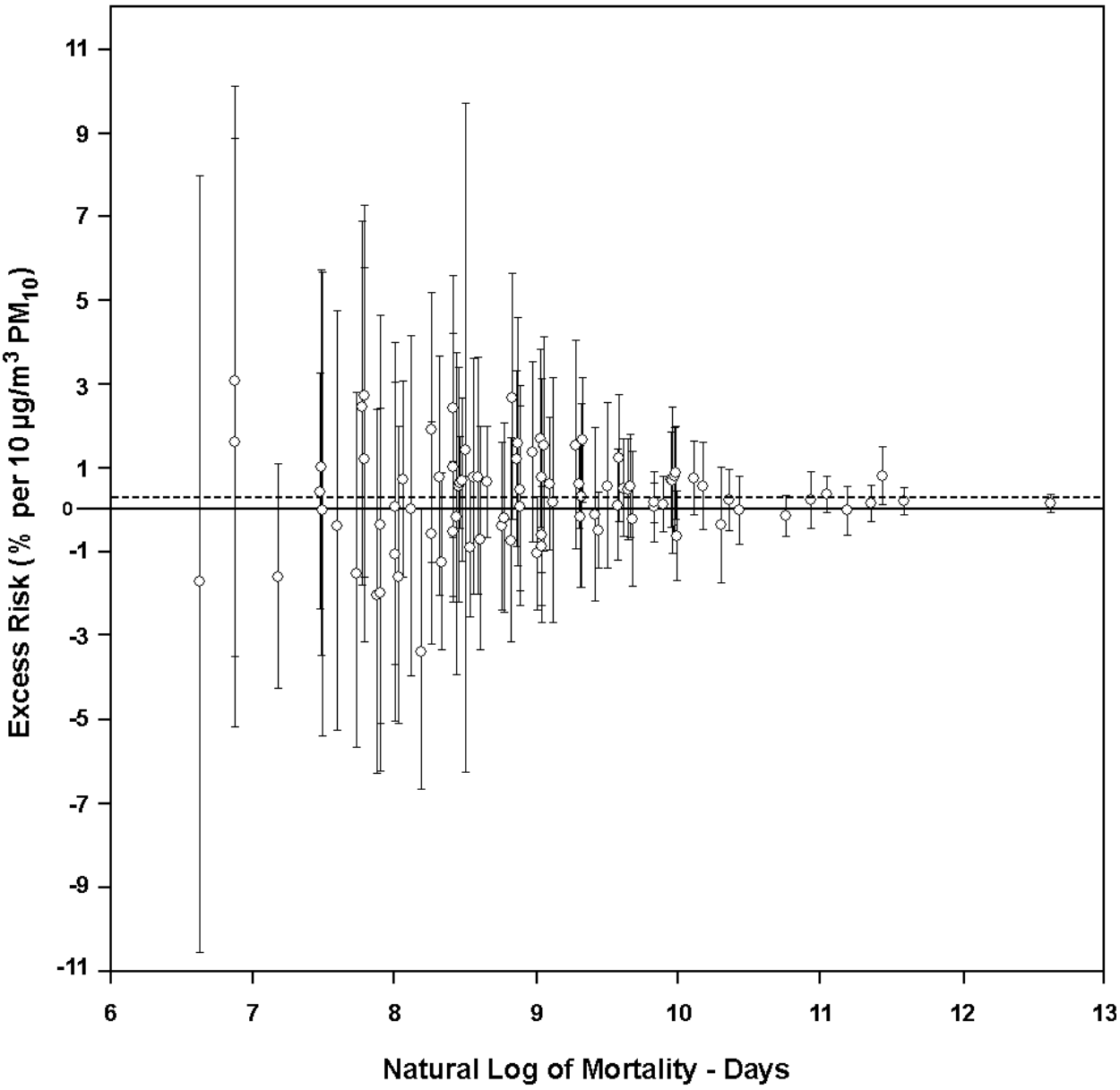

Figure 8-21. An EPA-derived plot showing relationship of PM_{10} total mortality effects estimates and 95% confidence intervals for all cities in the Dominici et al. (2000a; 2003) NMMAPS 90-cities analyses in relation to study size (i.e., the natural logarithm or numbers of deaths times days of PM observations). Note the generally narrower confidence intervals for more homogeneously positive effects estimates as study size increases beyond about ln (mortality-days) = 9.0 (i.e., beyond about 8,000 deaths-days of observation). The dashed line depicts the overall nationwide effect estimate (grand mean) of approximately 0.28% per 10 µg/m^3 PM_{10} for models with no co-pollutants.

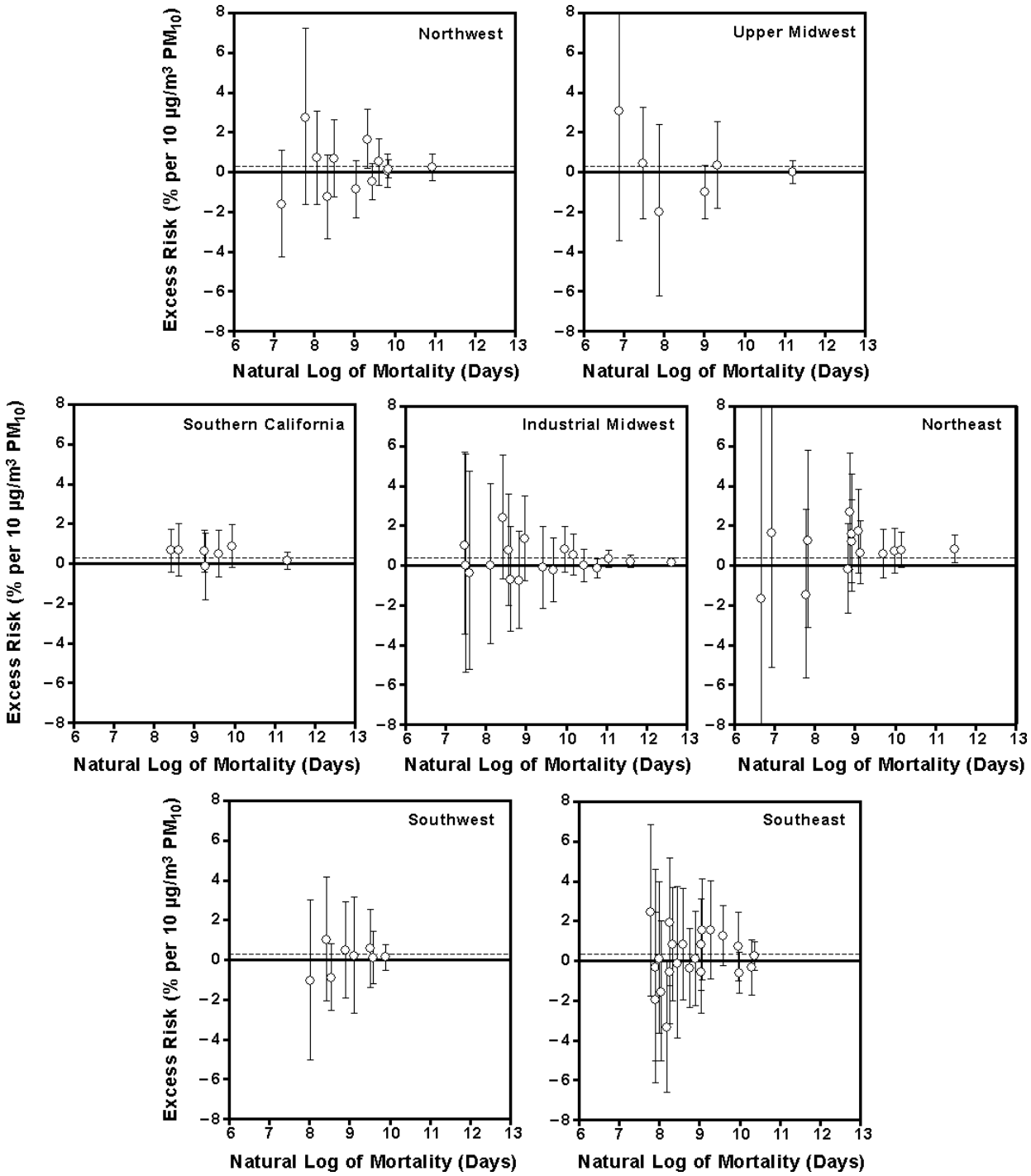

Figure 8-22. The EPA-derived plots showing Dominici et al. (2003) relationships of PM_{10}-mortality (total, nonaccidental) effects estimates and 95% confidence intervals to study size (defined as in Figure 8-10) for cities broken out by regions as per the NMMAPS regional analyses of Samet et al. (2000a,b). Dashed line on each plate depicts overall nationwide effect estimate (grand mean) of approximately 0.28% per 10 µg/m^3 PM_{10} for models with no co-pollutants.

all clearly exceed the overall nationwide grand mean indicated by the dashed line. On the other hand, the smaller study-size Northeast cities (with much wider confidence intervals at log < 8) show much greater heterogeneity of effects estimates and less precision. Also, most of the estimates for larger study-size (log > 9) cities in the industrial midwest are positive and several statistically significant, so that an overall significant regional risk is plausible there as well. There may even be some tendency for relatively large risks for some cities with small study sizes and wide confidence intervals in the industrial midwest, and further investigation of that would be of interest. The plot for Southern California in Figure 8-22 clearly shows a rather consistent estimate of effect size and width of the confidence intervals across cities of varying study-size. All risk estimates are positive and most are significant at $p \leq 0.05$ or nearly so for the Southern California cities. For Northwestern cities plotted in Figure 8-22, the value for Oakland, CA (at ca. log 9.5) is notable (it being very positive and significant), whereas many but not all of the other cities have positive effect estimates not too far off the nationwide grand mean, but with sufficiently wide confidence intervals so as not to be statistically significant at $p \leq 0.05$. The Southwestern cities, too, mostly appear to have effect sizes near the nationwide mean, but with confidence intervals too wide to be significant at $p \leq 0.05$. The "Other" (non-industrial or "Upper," as per NMMAPS) Midwest cities and the Southeastern cities in Figure 8-22 show more heterogeneity, although most of the larger study size cities (log $\geq$ 9.0) tend to be positive and not far off the nationwide mean (even though not significant at $p \leq 0.05$). Given the wide range of effects estimates and confidence intervals seen for Southeastern cities, further splitting of the region might be informative.

In fact, closer reexamination of results for each of the regions may reveal interesting new insights into what factors may account for any apparent disparities among the cities within a given region or across regions. Several possibilities readily come to mind. First, cursory inspection of the mean PM_{10} levels shown for each city in (Samet et al., 2000b; Appendix A) suggests that many of the cities showing low effects estimates and wide confidence intervals tend to be among those having the lowest mean PM_{10} levels and, therefore, likely the smallest range of PM_{10} values across which to distinguish any PM-related effect, if present. It may also be possible that those areas with higher $PM_{2.5}$ proportions of PM_{10} mass (i.e., larger percentages of fine particles) may show higher effects estimates (e.g., in Northeastern cities) than those with higher coarse-mode fractions (e.g., as would be more typical of Southwestern cities). Also, more

industrialized cities with greater fine-particle emissions from coal combustion (e.g., in the industrial Midwest) and/or those with high fine-particle emissions from heavy motor vehicle emissions (e.g., typical of Southern California cities) may show larger PM_{10} effects estimates than other cities. Lastly, the extent of air-conditioning use may also account for some of the differences, with greater use in many Southeastern and Southwestern cities perhaps decreasing actual human exposure to ambient particles present versus higher personal exposure to ambient PM (including indoors) in those areas where less air-conditioning is used (e.g., the Northeast and industrial Midwest).

8.4.7.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies

Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of U.S. cities to allow considerable resolution of regional PM effects within the "lower 48" states, but an attempt was made to take this approach to a much more detailed level in the Cohort Reanalysis studies than in NMMAPS. There were: 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in the original Pope et al. (1995) ACS analyses and in the HEI reanalyses using the original data; and 63 cities with $PM_{2..5}$ data and 144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis team. The relatively large number of data points utilized in the HEL reanalyses effort and additional analyses allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers.

The patterns for $PM_{2.5}$ and sulfates are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski et al., 2000; Figure 18) had peak levels around Chicago - Gary, in the eastern Kentucky - Cleveland region, and around Birmingham AL, with elevated but lower $PM_{2.5}$ almost everywhere east of the Mississippi, as well as southern California. This is similar to the modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated SO_2 concentrations was the Cleveland - Pittsburgh region. Secondary sulfates in particles derived from local SO_2 appeared more likely to be important in the industrial midwest, south from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia, and southwest Pennsylvania, possibly related to combustion of high-sulfur fuels.

The overlay of mortality with air pollution patterns is also of much interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewski et al., 2000; Figure 21) was highest from southern Ohio to northeastern Kentucky/West Virginia, but also included a significant association over most of the industrial midwest. This was reflected, in diminished form, by the sulfates and SO_2 maps (Krewski et al., 2000; Figures 19 and 20), where there appeared to be a somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that, while SO_2 was an important precursor of sulfates in this region, there may also be some other (non-sulfur) contributors to associations between $PM_{2.5}$ and long-term mortality, encompassing a wide area of the North Central Midwest and non-coastal Mid-Atlantic region.

The apparent differences in PM_{10} and/or $PM_{2.5}$ effect sizes across different regions should not be attributed merely to possible variations in measurement error or other statistical artifact(s). Some of these differences may reflect: real regional differences in particle composition or co-pollutant mix; differences in relative human exposures to ambient particles or other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in regional population); or other important, as of yet unidentified PM effect modifiers.

In their reanalyses of daily mortality in eight Canadian cities, Burnett and Goldberg (2003) report positive estimates of heterogeneity of particulate effects across cities using LOESS, whereas negative estimates of heterogeneity were obtained using natural splines. They stated that this finding was due to the reduction in effect estimate using natural splines that resulted in smaller observed variation in effect estimates across cities in addition to the increased within-city estimate error compared to models using LOESS for time and weather. However, Burnett and Goldberg (2003) ultimately concluded that evidence from their study is insufficient to conclude that the PM association with mortality varies across Canadian cities.

8.4.8 New Assessments of Measurement Error Consequences

8.4.8.1 Theoretical Framework for Assessment of Measurement Error

Since the 1996 PM AQCD, advances have been made in conceptual framework development to investigate effects of measurement error on PM health effects estimated in time-series studies. Several new studies evaluate the extent of bias caused by measurement errors under 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.

Marcus and Chapman (1998) 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; and 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 FP health effects are likely underestimated, although the magnitude of bias due to the analytical measurement error is not very large.

Zeger et al. (2000) illustrated the implication of the classical error model and the Berkson error model (i.e., $X = W + U$) in the context of time-series study design. Their simulation of the classical error model with two predictors, with various combinations of error variance and correlation between the predictors/error terms, showed results similar to those reported by Zidek et al. (1996). Most notably, for the transfer of the effects of one variable to the other (i.e., error-induced confounding) to be large, the two predictors or their errors must to be substantially

correlated. Also, for the spurious association of a null predictor to be more significant than the true predictor, their measurement errors have to be extremely negatively correlated—a condition not yet seen in actual air pollution data sets.

Zeger et al. (2000) also laid out a comprehensive framework for evaluating effects of exposure measurement error on estimates of air pollution mortality relative risks in time-series studies. The error, i.e., the difference between personal exposure and a central station's measurement of ambient pollutant concentration, was decomposed into three components: (1) the error due to having aggregate rather than individual exposure; (2) the difference between the average personal exposure and the true ambient concentration level; and, (3) the difference between the true and measured ambient concentration level. By aggregating individual risks to obtain expected number of deaths, they showed that the first component of error (the aggregate rather than individual) is a Berkson error, and, therefore is not a significant contributor to bias in the estimated risk. The second error component is a classical error and can introduce bias if there are short-term associations between indoor source contributions and ambient concentration levels. Recent analysis, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000) and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship between the ambient concentration and the nonambient components of personal exposure to PM. Still, a bias could arise due to the difference between the personal exposure to ambient PM (indoors plus outdoors) and the ambient concentration. The third error component is the difference between the true and the measured ambient concentration. According to Zeger et al. the final term is largely of the Berkson type if the average of the available monitors is an unbiased estimate of the true spatially averaged ambient level.

Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to estimate the second error component and its influence on estimated risks. The correlation coefficient between the error (the average population PM_{10} total exposure minus the ambient PM_{10} concentration) and the ambient PM_{10} concentration was estimated to be −0.63. Since this correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the regression of mortality on z_t, the daily ambient concentration) will tend to underestimate the coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on $\bar{x}_t$, the daily average total personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then proceeded to assess the size of the bias that will result from this exposure misclassification, using daily ambient

concentration, z_t. As shown in Equation 9, the daily average total personal exposure, $\bar{X}_t$, can be separated into a variable component, $\theta_1 z_t$, dependent on the daily ambient concentration, z_t, and a constant component, θ_o, independent of the ambient concentration:

$$\bar{X}_t = \theta_0 + \theta_1 z_t + \epsilon_t \quad (8\text{-}5)$$

where ϵ_t is an error term.

If the nonambient component of the total personal exposure is independent of the ambient concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to the ambient concentration. (The ambient component of personal exposure includes exposure to ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated indoors.) In this well-known approach to adjust for exposure measurement error, called regression calibration (Carroll et al., 1995), the estimate of β_x has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$. Thus, for the regression calibration, the value of β_x (based on the total personal exposure) does not depend on the total personal exposure but is given by β_z, based on the ambient concentration, times θ_1, the ratio of the ambient component of personal exposure to the ambient concentration. A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

Zeger et al. (2000) used Equation 9, with $\hat{\theta}_o = 59.95$ and $\theta_1 = 0.60$, estimated from the PTEAM data, to simulate values of daily average personal exposure, x^*_t, from the ambient concentrations, z_t, for PM_{10} in Riverside, CA, 1987-1994. They then compared the mean of the simulated $\hat{\beta}_x$ s, obtained by the series of log-linear regressions of mortality on the simulated x^*_t, with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the log-linear regression of mortality directly on z_t. The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$ is very close to $\theta 1 = 0.60$. Dominici et al. (2000b) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical model. Their findings were qualitatively similar in that was close to $/\theta_1$. Thus, it appears that the bias is very close to θ_1, which depends not on the total personal exposure but only on the ratio of the ambient component of personal exposure to the ambient concentration.

Zeger et al. (2000), in the analyses described above, also suggested that the error due to the difference between the average personal exposure and the ambient level (the second error type described above) is likely the largest source of bias in estimated relative risk. This suggestion at least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed relatively high site-to-site correlation ($\approx$ 0.6-0.9), a similar extent of site-to-site correlation for other pollutants is not necessarily expected. Ito et al. (2000) estimated site-to-site correlations (after adjusting for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint temperature, and relative humidity, using multiple stations' data from seven central and eastern states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles, these variables could be categorized into three groups in terms of the extent of correlation: weather variables ($r > 0.9$); O_3, PM_{10}, NO_2 (r: 0.6-0.8); CO and SO_2 ($r < 0.5$). These results suggest that the contribution from the third component of error, as described in Zeger et al. (2000), would vary among pollution and weather variables. Furthermore, the contribution from the second component of error would also vary among pollutants; i.e., the ratio of ambient exposure to ambient concentration, called the attenuation coefficient, is expected to be different for each pollutant. Some of the ongoing studies are expected to shed some light on this issue. However, more information is needed on attenuation coefficients for a variety of pollutants.

With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999), show reasonably good correlation ($r = 0.6$ to 0.9) between ambient PM concentrations and average population PM exposure, lending support for the use of ambient data as a surrogate for personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore, fine particles are expected to show even better site-to-site correlation than PM_{10}. Wilson and Suh (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for $PM_{10-2.5}$ ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger mortality associations for fine particles than coarse particles found in the Schwartz et al. (1996a) study may be due in part to larger measurement error for coarse particles.

However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle association with mortality is a "false positive", but rather, whether the weaker mortality

association with coarse particles is a "false negative." Carrothers and Evans (2000) also investigated the joint effects of correlation and relative error, but they specifically addressed the issue of fine (FP) versus coarse particle (CP) effect, by assuming three levels of relative toxicity of fine versus coarse particles (β_{FP} / β_{CP} = 1, 3, and 10) and, then, evaluating the bias, (B = $\{E[\beta_{F'}]/ E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e., B=1) as long as FP and CP are measured with equal precision, but, if, for example, FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e., B > 1); (2) when FP is more toxic than CP (i.e., β_{FP}/β_{CP} = 3 and 10), however, the equal precision of FP and CP results in downward bias of FP (B < 1), implying a relative overestimation of the less toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more so as the correlation between FP and CP increases. They also applied this model to real data from the Harvard Six Cities Study, in particular, the data from Boston and Knoxville. Estimation of spatial variability for Boston was based on external data and a range of spatial variability for Knoxville (since there was no spatial data available for this city). For Boston, where the estimated FP-CP correlation was low (r = 0.28), estimated error was smaller for FP than for CP (0.85 versus 0.65, as correlation between true versus error-added series), and the observed FP to CP coefficient ratio was high (11), the calculated FP to CP coefficient ratio was even larger (26)-thus providing evidence against the hypothesis that FP is absorbing some of the coefficient of CP. For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than for CP (0.9 versus 0.75), and the observed FP to CP coefficient ratio was 1.4, the calculated true FP to CP coefficient ratio was smaller (0.9) than the observed value, indicating that the coefficient was overestimated for the better-measured FP, while the coefficient was underestimated for the worse-measured CP. Since the amount (and the direction) of bias depended on several variables (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity), the authors concluded "...for instance, it is inadequate to state that differences in measurement error among fine and coarse particles will lead to false negative findings for coarse particles".

Fung and Krewski (1999) conducted a simulation study of measurement error adjustment methods for Poisson models, using scenarios similar to those used in the simulation studies that investigated implication of joint effects of correlated covariates with measurement error. The

measurement error adjustment methods employed were the Regression Calibration (RCAL) method (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and Stefanski, 1994). Briefly, RCAL algorithm consists of: (1) estimation of the regression of X on W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its estimate from (1), and conducting the standard analysis (i.e., regression); and (3) adjustment of the resulting standard error of coefficient to account for the calibration modeling. SIMEX algorithm consists of: (1) addition of successively larger amount of error to the original data; (2) obtaining naive regression coefficients for each of the error added data sets; and, (3) back extrapolation of the obtained coefficients to the error-free case using a quadratic or other function. Fung and Krewski examined the cases for: (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$; $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$., all with varying level of correlation (–0.8 to 0.8) with and without classical additive error, and also considering Berkson type error. The behaviors of naive estimates were essentially similar to other simulation studies. In most cases with the classical error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation was small), recovering underlying coefficients. In the presence of Berkson type error, however, even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5). This is the first study to examine the performance of available error adjustment methods that can be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX. Possible reasons why RCAL performed better than SIMEX in these scenarios were not discussed, nor are they clear from the information given in the publication. There has not been a study to apply these error adjustment methods in real time-series health effects studies. These methodologies require either replicate measurements or some knowledge on the nature of error (i.e., distributional properties, correlation, etc.). Since the information regarding the nature of error is still being collected at this time, it may take some time before applications of these methods become practical.

Another issue that measurement error may affect is the detection of threshold in time-series studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape of the exposure-response curve, and that such error could make the exposure-response curve to appear linear even when a threshold may exist. However, based on a simulation with realistic range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated that the

modern smoothing approach, LOESS, can adequately detect threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$) even with the presence of exposure error.

Other issues related to exposure error that have not been investigated include potential differential error among subpopulations. If the exposure errors are different between susceptible population groups (e.g., people with COPD) and the rest of the population, the estimation of bias may need to take such differences into account. Also, the exposure errors may vary from season to season, due to seasonal differences in the use of indoor emission sources and air exchange rates due to air conditioning and heating. This may possibly explain reported season-specific effects of PM and other pollutants. Such season-specific contributions of errors from indoor and outdoor sources are also expected to be different from pollutant to pollutant.

In summary, the studies that examined joint effects of correlation and error suggest that PM effects are likely underestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of coefficient) due to transferring of effects from other covariates require extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing methods. More data are needed to examine the exposure errors for other pollutants, since their relative error contributions will influence their relative significance in relative risk estimates.

8.4.8.2 Spatial Measurement Error Issues That May Affect the Interpretation of Multi-Pollutant Models with Gaseous Co-Pollutants

The measurement error framework put forth in Dominici et al. (2000) and Zeger et al. (2000) explicitly assumes that one of the error components has a Berkson error structure. As summarized in (Zeger et al., 2000, p. 421): "This Berkson model is appropriate when z represents a measurable factor [e.g., measured PM or another pollutant] that is shared by a group of participants whose individual [true] exposures x might vary because of time-activity patterns. For example, z might be the spatially averaged ambient level of a pollutant without major indoor sources and x might be the personal exposures that, when averaged across people, match the ambient level." This assumption is likely accurate for sulfates, less so for fine particles and for PM_{10}, and almost certainly incorrect for gases such as CO and NO_2 that may vary substantially on an intra-urban spatial scale with widely distributed local sources.

The usual characterization of longitudinal or temporal pollutant correlation may not adequately characterize the spatial variation that is the more important aspect of association in

evaluating possible Berkson errors. Temporal correlation coefficients, even across large distances (e.g., Ito et al., 2001) may be a consequence of large-scale weather patterns affecting the concentrations of many pollutants. Local concentrations for some pollutants with strong local sources and low regional dispersion (especially for CO and NO_2, and $PM_{10-2.5}$ to a lesser extent) may have somewhat smaller temporal correlations and much greater relative spatial variations than PM. Thus, individuals in a large metropolitan area may have roughly similar levels of PM exposure x on any given day for which the ambient average PM concentration z is an adequate surrogate, whatever their space-time activity patterns, residence, or non-residential micro-environments, while the same individuals may be exposed to systematically higher or lower concentrations of a co-pollutant than the spatial average of the co-pollutant. This violates the basic assumption of the Berkson error model that within each stratum of the measured (spatially averaged) level z, the average value of the true concentration x is equal to z, i.e.,

$$E\{ x \mid z \} = z, \tag{8-6}$$

where E{.} is the average or expected value over the population.

There are empirical reasons to believe that if the strata are chosen to be locations within a metropolitan area, some individuals far from local sources have consistently less exposure than the average ambient concentration (denoted p) for co-pollutants with local sources such as CO and NO_2, and $PM_{2.5}$, whose true exposure (denoted q) depends on the location of the person's residence or other micro-environment where most exposure occurs. For this group,

$$E\{ q \mid p \} < p, \tag{8-7}$$

while others in locations near the local source (such as a busy highway) have systematically higher exposure, so that

$$E\{ q \mid p \} > p. \tag{8-8}$$

There is a substantial and growing body of evidence that adverse health effects are associated with proximity to a major road or highway (Wjst et al., 1993; Monn et al., 2001;

Roemer and Van Wijnen, 2001). As shown below, there is good reason to believe that intra-city variation (even in $PM_{2.5}$) is substantial within some U.S. cities. If we assume for the sake of argument that concentrations of PM_{10} or $PM_{2.5}$ are relatively uniformly distributed, then associations of adverse health effects with proximity to a source cannot be readily attributed to a pollutant such as PM with a uniform spatial distribution. NO_2 is a pollutant often used to illustrate the spatial non-uniformity of the gaseous co-pollutants. Figure 8-23 from Monn et al. (1997) compares the concentrations of NO_2 and PM_{10} as a function of curbside distance in a moderately busy urban street in Zurich. The PM_{10} levels decrease only slightly with increasing distance, the decrease more likely being due to decreasing coarse particle than decreasing fine particle concentrations. The NO_2 concentrations show a much stronger seasonal dependence, decreasing rapidly with increasing distance in the summer and showing little decrease with distance in the winter. However, the belief that $PM_{2.5}$ is spatially uniform should also not be accepted uncritically, as recent analyses for 27 U.S. cities shown in Chapter 3 and Appendix 3A of this document demonstrate.

The 90^{th} Percentile differences (P_{90}) between a pair of sites may provide a useful guide to the differences between monitor pairs (and by implication, personal exposure to fine particles) that might be reasonably expected within a metropolitan area. Shown below in Table 8-38 are the maximum, median, and minimum differences between monitor pairs, the monitor pairs at which the largest 90th percentile difference occurs (by reference to tables in Appendix 3A). Based on these differences, Table 8-39 shows cities to be "relatively homogeneous" (with $P90 < 10\ \mu g/m^3$) and "relatively heterogeneous" (if $P90 \geq 10\ \mu g/m^3$). The results in Appendix 3A and Table 8-38 show a variety of spatial patterns of association of $PM_{2.5}$ within a Metroplitan Statistical Area (MSA). There may be some discernable regional differences; but, because many major population centers are not represented in Appendix 3A, further investigation is likely warranted.

The results shown here provide clear evidence that fine particle concentrations may be less homogenous in at least some MSAs than has been previously assumed. This provides support for earlier studies using TSP and PM_{10} cited below. As noted in Chapter 3, these differences may not be strictly related to the distance between monitors, especially where topography and sources of primary PM play a role. In many eastern sites, however, particle distribution may be more substantially governed by regional rather than by local sources.

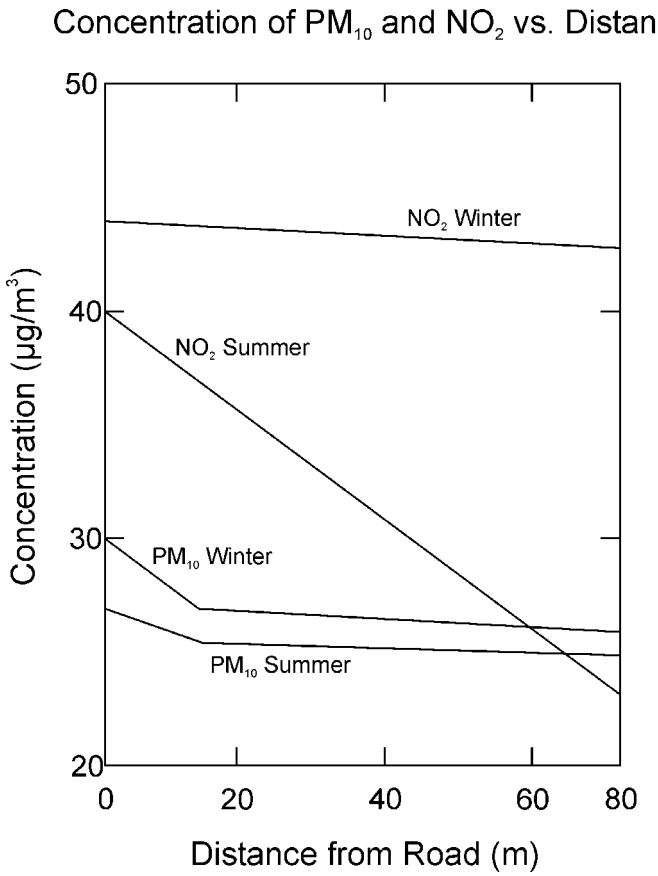

Figure 8-23. Concentration of PM_{10} and NO_2 versus distance.

Source: Monn et al. (2000).

Several recent studies have examined the role of spatial siting of monitors on the estimation of PM effects. Ito et al. (1995) examined the ability of single-site versus multi-site averages to best estimate total mortality versus PM_{10} in Cook County (Chicago), IL and Los Angeles County, CA. In order to have a sufficiently large sample size to detect effects, Ito et al. used six PM_{10} sites in Cook County (Chicago), IL and four sites in Los Angeles County, CA. A sinusoidal model was used to account for temporal components, although spline or LOESS methods would now be used. Only one Cook County site had every-day PM samples, and the others as well as the Los Angeles sites had a one-in-six-day sampling schedule. The monitor sites were located in urban and suburban settings, according to the State's objectives. Three of the Los Angeles sites were located in residential areas and one was located in an area

TABLE 8-38. MAXIMUM, MEAN, 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

City	N Sites	Maximum (Pair)	Mean	Minimum
Pittsburgh, PA	11	21.0 (CJ)	8.4	4.2
Los Angeles, CA	6	18.2 (CF)	13.1	6.2
Seattle, WA	5	17.9 (AE)	9.8	3.6
	4 (w/o A) *	8.5 (CE)	6.8	3.6
Riverside-San Bernardino, CA	5	17.8 (BC)	12.3	6.6
Birmingham, AL	5	15.2 (AE)	10.6	6.7
St. Louis, MO	11	15.2 (AH)	6.7	2.8
Cleveland, OH	8	14.3 (BG)	8.6	3.3
Detroit, MI	10	13.8 (DI)	8.1	5.0
Atlanta, GA	7	13.2 (EG)	9.4	5.3
	6 (w/o G) *	10.8 (CF)	8.1	5.3
Salt Lake City, UT	6	11.4 (CF)	7.5	4.4
Gary, IN	4	11.3 (BC)	7.8	4.2
Chicago, IL	11	11.3 (EJ)	6.8	3.5
San Diego, CA	4	11.0 (CD)	9.1	6.3
Steubenville, OH	5	10.0 (BE)	7.9	6.2
Washington, DC	6	9.1 (DF)	6.6	3.5
	5 (w/o F)	7.7 (AE)	5.8	3.5
Boise, ID	4	8.8 (BD)	5.3	3.8
Philadelphia, PA	7	7.5 (BC)	6.7	3.3
Kansas City, MO	6	6.5 (CF)	4.2	1.9
Portland, OR	4	6.5 (AB)	4.8	4.1
Grand Rapids, MI	4	6.1 (BC)	4.8	3.1
Louisville, KY	4	6.0 (AC)	5.2	3.8
Dallas, TX	7	5.5 (EG)	3.4	1.9
Milwaukee, WI	8	5.0 (FH)	3.7	2.8
Tampa, FL	4	5.0 (BD)	4.1	3.1
Norfolk, VA	5	5.0 (AC)	3.6	2.6
Columbia, SC	3	3.3 (AB)	3.1	2.8
Baton Rouge, LA	3	2.9 (AC)	2.7	2.5

* Without one site > 100 km from the others.

Source: Based on Chapter 3 and Appendix 3A analyses.

TABLE 8-39. 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	
Pittsburgh, PA		Norfolk, VA	
St. Louis, MO		Louisville, KY	
Steubenville, OH		Philadelphia, PA	
		Tampa, FL	
		Washington, DC	
	Seattle, WA (with A)		Seattle, WA (w/o A)

zoned for commercial use. One of the Cook County sites was classified as residential, two as commercial, and three as industrial. One of the Chicago sites was intended to monitor population exposure, three to monitor maximum concentrations, and two to monitor both maximum concentrations and personal exposure. There was considerable variation among the distribution of PM_{10} in Cook County (Chicago), IL sites, and among Los Angeles County, CA sites, especially at the upper end of the distribution. The sites were temporally correlated, 0.83 to 0.63 in Cook County, 0.9 to 0.7 in Los Angeles (except for one site pair), across distances of 4 to 26 miles. The Cook County mortality estimates were better estimated by some single-site estimates (Site 2 with everyday data, N = 1251) than by an average using all available data with missing values estimated from non-missing data (N = 1357). The every-six-day subsamples from Site 1 (N = 281) and Site 2 (lag 0, N = 246) were better predictors, and from Site 4 (N = 243) and Site 6 (N = 292) about as good predictors of mortality as the corresponding every-six-day averages (N = 351). In Los Angeles, only Site 4 (N = 349) was about as predictive as the spatial averages (N = 405).

Lipfert et al. (2000a) examined the relationship between the area in which mortality occurred among residents and the locations of monitoring sites or averages over monitoring sites for several particle size components and particle metrics. The mortality data were located for Philadelphia, PA, for three additional suburban Philadelphia counties, for Camden, NJ and other New Jersey counties in the Philadelphia – Camden MSA. A single site was used for fine and coarse particles from the Harvard School of Public Health monitors. Additional PA and NJ thoracic particle data were available for 2 to 4 stations and results averaged for at least two stations reporting data. The authors conclude that mortality in any part of the region may be associated with air pollution concentrations or average concentrations in any other part of the region, whether particles or gases. The authors suggest two interpretations: (a) the associations of mortality with pollution were random (from carrying out multiple significance tests) and not causal, or (b) both particles and gaseous pollutants have a broad regional distribution. The authors note that interpretation (b) may lead to large uncertainties in identifying which pollutant exposures for the population are primarily responsible for the observed effects. These data could be studied further to evaluate smaller-scale spatial relationships among health effects and gases.

Lippmann et al. (2000) evaluated the effects of monitor siting choice using 14 TSP monitoring stations in Detroit, MI, and nearby Windsor, ON, Canada. The stations operated from 1981-1987 with almost complete data. When a standard log-linear link Poisson regression model for mortality was fitted to TSP data for each of the 14 sites, the relative risk estimates were similar for within-site increments of 5^{th} to 95^{th} percentiles, generally highest and positive at lag day 1, but not statistically significant except for site "w" (site 12, south of the urban center of Wayne County) and nearly significant at sites "f" (west of the city of Detroit), "g" (south of the city) and "v" (suburban site in northwestern Wayne County, MI, generally "upwind" of the urban center). However, as the authors note, all of the reported relative risks are for site-specific increments, which vary by a factor of about 2.5 over the Wayne County - Windsor area. When converted to a common increment of 100 $\mu g/m^3$ TSP, the largest excess risks are found when the monitor used in the model is "f" (4.5%), "v" (4.2%), or "w" (3.8%), which also show the most significant effects among the 14 monitors. As the authors note, ". . . the distributional increments [used] to calculate relative risk tend to standardize the scale of relative risks. This actually makes sense in that if there is a concentration gradient of TSP within a city, and if the various TSP concentrations fluctuate together, then using a site with a low mean TSP for time-

series analysis would result in a larger coefficient. This result does warn against extrapolating the effects from one city to an other using a raw regression coefficient [excess relative risk]"

Other recent studies also point out other aspects of intra-urban spatial variation in PM concentrations. Kinney et al. (2000) note that, in a study of personal and ambient $PM_{2.5}$ and diesel exhaust particle (DEP) exposure in a dense urban area of New York City, $PM_{2.5}$ concentrations showed only a moderate site-to-site variation (37 to 47 $\mu g/m^3$), probably due to broader regional sources of $PM_{2.5}$, whereas elemental carbon concentrations (EC) showed a four-fold range of site-to-site variations, reflecting the greater local variation in EC from DEP.

Several PM health studies for Seattle (King County), WA (e.g., Levy et al., 2001a, for out-of-hospital primary cardiac arrests) found few statistically significant relationships, attributed by the authors in part to the fact that Seattle has topographically diverse terrain with local "hot spots" of residential wood burning, especially in winter. Sheppard et al. (2001) explored reasons for these findings, particularly focusing on adjustments for location by use of a "topographic index" that includes "downstream" normal flow of wood smoke from higher elevations and trapping of wood smoke in topographic bowls or basins even at higher elevations. They also adjusted for weather using a "stagnation index" (the average number of hours per day with wind speed less than the 25^{th} percentile of wind speeds) and temperature, as well as interaction terms for stagnation on hilltop sites and temperature at suburban wood-smoke-exposed valley sites.

The adjustments for exposure measurement error based on methods developed in Sheppard and Damian (2000) and Sheppard et al. (2001) had little effect on effect size estimates for the case-crossover study (Levy et al., 2001a), but may be useful in other studies where localized effects are believed to be important, particularly for the gaseous co-pollutants. Bateson and Schwartz (2001) note that investigators should be careful when making assumptions about the reference exposure distribution, in that the issue of comparability of the case and reference groups is a general one for case-cross over analyses.

Daniels et al. (2001) evaluated relative sources of variability or heterogeneity in PM_{10} monitoring in Pittsburgh, PA in 1996. The area is data-rich, having 25 monitors in a ~40 by 80 km rectangle. The authors found no isotropic spatial dependence after accounting for other sources of variability, but an indication of heterogeneity in the variability of the small-scale processes over time and space and heterogeneity in the mean values and covariate effects across sites. Important covariates included temperature, precipitation, wind speed and direction. The

authors concluded that significant unmeasured processes might be in operation. These methods should also be useful in evaluating spatial and temporal variations in gaseous co-pollutants, where small-scale processes are important.

8.4.8.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in Multi-Pollutant Models.

The Zeger et al. (2000) discussion may be interpreted as addressing the extent to which the apparent lack of a $PM_{10-2.5}$ effect in models with both fine and coarse particles demonstrates a "false negative" due to larger measurement error of coarse particle concentrations. However, a more important question may involve the relative attenuation of estimated effects of $PM_{2.5}$ and gaseous co-pollutants, especially those such as CO that are known to be highly correlated with $PM_{2.5}$. Tables 1 and 2 in (Zeger et al., 2000) may be particularly relevant here. The evidence discussed in this chapter supports the hypothesis that PM has adverse health effects, but leaves open the question as to whether the co-pollutants have effects as well when their exposure is measured much less accurately than that of the PM metric. If both the PM metric and the co-pollutant have effects, Table 1 of Zeger et al. (2000) shows that the co-pollutant effect size estimate may be greatly attenuated and the PM effect size estimate much less so, depending on the magnitude of correlation between the true PM and gaseous pollutant exposures and the correlation between their measurement errors. One would expect that $PM_{2.5}$, CO, and NO_2 would often have a high positive correlation and their "exposure measurement errors" would also be positively correlated if PM and the gaseous pollutants were positively correlated due to common activity patterns, weather, and source emissions. Thus, the line with $corr(x_1,x_2) = 0.5$, $var(\delta_1) = 0.5$, $var(\delta_2) = 2$, $corr(\delta_1, \delta_2) = 0.7$ seems appropriate. This implies that the estimated effect of the more accurately measured pollutant is 64% of the true value, and that of the less accurately measured pollutant is 14% of the true value. In view of the substantially greater spatial heterogeneity of traffic-generated ambient pollutants such as CO and NO_2, and the relative (though not absolute) regional spatial uniformity of ambient $PM_{2.5}$ in some cities, but not in others, it is likely that effect size estimates in multi-pollutant models are attenuated downward to a much greater extent for the gaseous co-pollutants than for the PM metric in some cities, but not in others. This may explain part of the heterogeneity of findings for multi-pollutant models in different cities. Low effect size estimates for the gaseous co-pollutants in a multi-pollutant model should be interpreted cautiously. The representativeness of the monitoring sites for

population exposure of both the particle metrics and gaseous pollutants should be evaluated as part of the interpretation of the analysis. Indices such as the maximum 90th percentile of the absolute difference in concentrations between pairs of sites as well as the median cross-correlation across sites may be useful for characterizing for spatially heterogeneity of gaseous co-pollutants as well as for fine particles.

8.4.8.4 Air Pollution Exposure Proxies in Long-Term Mortality Studies

The AHSMOG Study of mortality (Abbey et al., 1999; McDonnell et al., 2000), the Harvard 6-Cities Study of mortality (Dockery et al, 1993), the ACS Study (Pope et al., 1995), and the VA/Washington Univ. Study (Lipfert et al., 2000b) together provided a major step forward in the assessment of the long-term effects of air pollution. These cohort studies responded to many of the major criticisms of the prior cross-sectional mortality studies, while largely confirming the results of those prior studies. In particular, unlike the ecological cross-sectional studies, these new cohort studies had individual-level information about the members of the study cohort, allowing the analysis to more properly control for other major factors in mortality, such as smoking and socio-economic factors.

While several of these studies made use of newly available fine particle ($PM_{2.5}$) mass data to derive useful estimates of health effects of $PM_{2.5}$ well before it was routinely measured, these studies utilized air pollution exposure information in a manner similar to past studies, i.e., the studies used central site metropolitan area (MA) spatial and time averages of air pollution exposures, rather than exposure information at the individual level. For this reason, the AHSMOG, Harvard Six-Cities, ACS, and VA/Washington Univ. studies have been term "semi-individual" cohort studies of air pollution.

The AHSMOG Study

Although this study covers a large number of years (1977-1992 in Abbey et al., 1999), it is much more limited in the availability of actually-observed versus estimated particle metrics. Prior to 1987, PM_{10} could only be estimated from TSP, not observed. Also, for more recent years, McDonnell et al. (2000) used participants who lived near an airport, so that $PM_{2.5}$, and $PM_{10-2.5}$ as the difference of PM_{10} and $PM_{2.5}$, could be estimated from airport visibility data using

methods described earlier (Abbey et al., 1995b). All this adds potential measurement error to the exposure estimates.

The Veterans' Administration/Washington University Study

The air pollution concentrations for participants' counties of residence at time of enrollment were used in analyses, rather than concentrations at the 32 VA hospitals in the final study. County-wide pollution variables for five particle metrics and three gaseous pollutants were used in the study, although TSP was most often the particle metric observed for the earlier years of the study (before 1975 up to1988), which are important in assessing pollution effects for many years of exposure. However, IPMN data for fine particles and sulfates were available for ca. 1979-1983, as in the ACS study. Effects on average mortality for the intervals 1976-1981, 1982-1988, and 1989-1996 were related to multi-year particle exposures for four long intervals: < 1975, 1975-1981, 1982-1988, and 1989-1996. TSP was used in the first three exposure intervals; PM_{10} in the most recent. This study examined "concurrent" exposures (same interval as average mortality), "causal" prior exposures (exposure interval precedes mortality interval), and "non-causal" PM versus mortality associations. The mortality associations were also examined for $PM_{2.5}$, PM_{15}, and $PM_{15\text{-}2.5}$ for 1979-1981 and 1982-1984. This study uses essentially the same air pollution data as the ACS study, which should be adequate for characterizing fixed-site air pollution concentrations in the place of residence at the time of enrollment. However, if any participants moved away from the county where air pollution is measured, but were retained in the study because they continued in follow-ups at the same clinic, then use of initial residence location may not be an adequate proxy for actual exposure after initial enrollment.

Harvard Six-Cities Air Pollution Exposure Data

In the Harvard Six Cities Study, ambient concentrations of fine particles ($PM_{2.5}$), total suspended particles (TSP), sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), and sulfate ($SO_4^{=}$) were measured at a centrally located air monitoring station within each of six communities. Long-term mean concentrations for each pollutant were calculated for periods that were consistent among the six cities, but not across pollutants. The original epidemiologic analysis characterized ambient air quality as long-term mean concentrations of total particles

(TSP) (1977-1985), inhalable and fine particles (1979-1985), sulfate particles (1979-1984), aerosol acidity (H^+) (1985–1988), sulfur dioxide (1977-1985), nitrogen dioxide (1977-1985), and ozone (1977-1985), as follows:

Particles: Mean PM concentrations were reported for four classifications of particles in each of the six cities: TSP (particles with aerodynamic diameters up to 50 μm), inhalable particles, fine particles, and sulfate particles. Values of mass for TSP and sulfate particles were determined from 24-h high-volume samplers. Inhalable particle mass was calculated from coarse and fine particle mass, which had been determined from 24-h sample pairs collected by dichotomous samplers. In these, the fine particle channel collected particles smaller than about 2.5 μm and the measurement was recorded directly as fine particle (FP) mass. The coarse particle channel collected particles 2.5 μm to 10 or 15 μm in aerodynamic diameter (the upper bound measurement depended on the inlet size used at the time).

Acidity: Aerosol acidity (H^+) was measured for about one year in each city. However, measurements were conducted in only two cities at a time. Thus, it was not possible to compare acidity for a common time period. Furthermore, the acidity data were not linked with particle data in the same city. Thus, intercity and inter-pollutant comparisons of H^+ in this study were confounded by inter-annual variability.

Gases: The gases (SO_2, NO_2, and O_3) were measured (in parts per billion) hourly by conventional continuous monitors.

ACS Study Air Pollution Exposure Data

In the ACS Study (Pope et al., 1995), two measures of particulate air pollution, fine particles, and sulfate, but no gaseous pollutants were considered. The mean concentration of sulfate air pollution by metropolitan area (MA) during 1980 was estimated using data from the EPA Aerometric Information Retrieval System (AIRS) database. These means were calculated as the averages of annual arithmetic mean 24-h sulfate values for all monitoring sites in the 151 MA's considered. The median concentration of fine particles between 1979 and 1983 was estimated from the EPA's dichotomous sampler network. These estimates of fine particle levels

had been used previously in a population-based cross-sectional mortality study of 50 MA's. Gaseous co-pollutants were not considered in Pope et al's original ACS analysis.

Six-City Study and ACS Exposure Data Strengths and Weaknesses

In each of these studies, there was a single mean pollution concentration assigned for each city for each pollutant for the entire follow-up period considered. Concentrations were not broken into each year or sub-groups of years (e.g., 5 year averages), largely because data were not available in this form. This may represent a potential weakness, as a single number could not accurately account for the different exposures in different years of follow-up. It is possible, however, that the simultaneous or immediately preceding years alone might not as well represent the effects of long-term pollution exposure.

The ACS analysis also uses metropolitan area (MA) pollutant concentrations for air pollution exposure estimates, rather than individual level measurements. Thus, spatial variability in air pollution levels and potential effects of different housing infiltration rates were not addressed as potential factors in exposure variability. However, individual exposure data would be economically impractical for such large cohorts, and the use of more localized measurements (e.g., by county) might well lead to more error, due to day-to day mobility between counties by individuals (e.g., to work and back) and changes of specific residence within an MA over time. Thus, the MA average may actually be the best metric that can be developed in the absence of individual level exposure data.

Another notable weakness of the original ACS Study was that only two PM air pollution metrics were considered. Thus, this study did not consider the potentially confounding influences of gaseous air pollutants or other particle indicators.

These two studies' analyses assign the subjects' residence MA on the basis of where they were enrolled, which can lead to exposure errors if the subjects moved to another MA during the follow-up period. However, a recent reanalysis of the Six Cities Study cohort (Krewski et al., 2000) indicates that mobility in these older populations is limited, with only 18.5% leaving the original city of enrollment over subsequent decades.

The HEI Reanalysis of the ACS Study

The HEI Reanalysis of these two cohort studies (Krewski et al, 2000) confirmed the databases used in these two studies, but also developed new exposure data for the ACS Study cohort. In particular, data for the gaseous pollutants (for the year 1980) were added to the analysis. Table 8-38 displays summary data for the most recent data available for the analysis of the ACS cohort (Pope et al., 2002). The variables noted with the data source "HEI" were added to the analysis during the HEI reanalysis. These HEI results largely confirmed the original ACS analysis results for PM, but also indicated that SO_2 was also correlated with U.S. mortality.

The 16-Year Follow-Up of the ACS Cohort

Table 8-40 also includes summaries of the pollutant data developed to provide exposure estimates for the latest 16-year follow-up analysis of the ACS cohort (Pope et al, 2002). These new data are similarly city-wide averages of all monitoring stations in the MA's considered, but for the entire period of follow-up (1982-1998), when possible. In addition, this new analysis has incorporated the new $PM_{2.5}$ air monitoring data collected routinely from 1999 onward. As a result, this new analysis has increased the analysis power both by extending the length of follow-up, and by adding significant new multiple and multi-year air pollution exposure data to the analysis.

8.4.9 Implications of Airborne Particle Mortality Effects

The public health burden of mortality associated with exposure to ambient PM depends not only on the increased risk of death, but also on the amount of life shortening that is attributable to those deaths. The 1996 PM AQCD concluded that confident quantitive determination of years of life lost to ambient PM exposure was not yet possible and life shortening may range from days to years (U.S. Environmental Protection Agency, 1996a). Now, some newly available analyses provide further interesting insights with regard to potential life-shortening associated with ambient PM exposures.

8.4.9.1 Short-Term Exposure and Mortality Displacement

A few studies have investigated the question of "harvesting," a phenomenon in which a deficit in mortality occurs following days with (pollution-caused) elevated mortality, due to

TABLE 8-40. 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).

depletion of the susceptible population pool. This issue is very important in interpreting the public health implication of the reported short-term PM mortality effects. The 1996 PM AQCD discussed suggestive evidence observed by Spix et al. (1993) during a period when air pollution levels were relatively high. Recent studies, however, generally used data from areas with lower, non-episodic pollution levels.

Schwartz (2000c; reanalysis 2003) separated time-series air pollution, weather, and mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) "intermediate" fluctuations; (3) "short-term" fluctuations. By varying the cut-off between the intermediate and short term, evidence of harvesting was sought. The idea is, for example, if the extent of harvesting were a matter of a few days, associations between weekly average values of mortality and air pollution (controlling for seasonal cycles) would not be seen. Schwartz's reanalysis using natural splines reported reductions in COPD mortality $PM_{2.5}$ risk estimates for longer time scale, suggesting that most of the COPD mortality was only displaced by a few weeks. However, for pneumonia, ischemic heart disease, and all cause mortality, the effect size increased, as longer time scales were included. For example, the percent increase in non-accidental deaths associated with a 25 $\mu g/m^3$ increase in $PM_{2.5}$ increased from 5.8% (95% CI: 4.5, 7.3) for the15-day window to 9.7% (95% CI: 8.2, 11.2) for the 60-day window. Note, however, that the 60-day time scale window is in the range of influenza epidemics. Some caution is therefore needed in interpreting risk estimates in this range.

Zanobetti et al. (2000b) used what they termed "generalized additive distributed lag models" (penalized splines using algorithm that did not require back-fitting were used for all the smoothing terms) 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 45 th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.

Zanobetti et al. (2001; reanalysis by Zanobetti and Schwartz, 2003) also applied the same concept described above (up to 41 lag days) to 10 cities from APHEA2 to estimate distributed lag PM_{10} mortality risks. They applied the covariate adjustment in a GAM model used in APHEA2 (Katsouyanni et al., 2001); and in reanalysis (Zanobetti and Schwartz, 2003), they also used penalized splines in addition to the GAM model with stringent convergence criteria. The

resulting city specific coefficients were pooled in the second-stage model taking into account heterogeneity across cities. The estimated shape of the distributed lag pooled across 10 cities showed a similar pattern to that from Milan data described above, with the second "hump" of smaller but positive coefficients between approximately 20 to 35 days. The results indicated that, compared to PM_{10} risk estimates obtained for the average of lag 0 and 1 days, the distributed lag estimates up to 40 days were about twice larger in both GAM and penalized splines models. For example, the combined distributed lag estimates for the 10 cities using penalized splines was 5.6% (95% CI: 1.5, 9.8), as compared to 2.9% (95% CI: 1.4, 4.4). It should be noted, however, that the results for individual cities varied. For example, the estimates for average of lag 0 and 1 days and the distributed lag model were comparable in Tel Aviv, whereas it was nearly seven times bigger for distributed lag model in Lodz. Thus, while these results do support the lack of mortality displacement up to 40-45 day period, the pattern of lagged associations may vary from city to city.

Smith et al. (1999), as part of their analysis of PM_{10}-mortality association in Birmingham, AL and Cook County, IL, also examined the existence of mortality displacement. Their model attempted to estimate the size of the frail population and the number of migrants into the frail population. PM_{10} was modeled to affect both the entry into the frail population and death. The latent variable structure was fitted through Bayesian techniques using Monte Carlo sampling. The resulting posterior mean for the frail population in Chicago was 765 (posterior s.d. = 189). The mean numbers of days lost as a result of 10 $\mu g/m^3$ increase in PM_{10} was estimated to be 0.079 day (posterior s.d. = 0.032). These results indicate that the frail population is small and therefore has short lifetime (less than 10 days) in that state. Consequently, the impact of PM (life shortening) had to be small. These results are not consistent with those suggested by Zanobetti or Schwartz studies described above.

Murray and Nelson (2000) used Kalman filtering to estimate hazard function of TSP in a state space model in the Philadelphia mortality data during 1973-1990. The model framework, which assumes harvesting effect, allows estimation of at-risk population and the effect of changes in air quality on the life expectancy of the at-risk population. The model was first verified by simulation. Combinations of TSP, linear temperature, squared temperature, and interaction of TSP and temperature were considered in six models. The size of at-risk (or frail) population estimated was about 500 people, with its life expectancy between 11.8 to 14.3 days,

suggesting that the hazard causing agent making the difference of 2.5 days in the at-risk population. These results are, taking into account the difference in population size between Philadelphia and Cook County, comparable with those obtained by Smith et al. described above. In both cases, the size of the frail population is small with short lifetime such that life-shortening by PM or any external stress for the frail population could not be long (more than a few days). These results are, again, in contrast to the results from the Zanobetti or Schwartz studies above or a frequency domain approach described below.

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 analysis (and reanalysis by Dominici et al., 2003) of real data from Philadelphia, regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger suggested that "harvesting-resistant" regression coefficients could be obtained by excluding coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of those coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, except perhaps the spectral analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients by frequency (*gain*) may be useful in evaluating the potentially frequency-dependent relationships among multiple time series. A few past examples in air pollution health effects studies include: (1) Shumway et al.'s (1983) analysis of London mortality analysis, in which they observed that significant coherence occurred beyond two week periodicity (they interpreted this as "pollution has to persist to affect mortality"); (2) Shumway et al.'s (1988) analysis of Los Angeles mortality data, in which they also found larger coherence in the lower frequency; (3) Ito's (1990) analysis of London mortality data in which he observed relatively constant gain (regression coefficient) for pollutants across the frequency range, except the annual cycle. These

results also suggest that associations and effect size, at least, are not concentrated in the very high frequency range.

Schwartz (2000c), Zanobetti et al. (2000b), Zanobetti et al., (2001; reanalysis by Zanobetti and Schwartz, 2003) and Zeger et al.'s analysis (1999; reanalysis by Dominici et al., 2003) all suggest that the extent of harvesting, if any, is not a matter of only a few days. Other past studies that used frequency domain analyses are also at least qualitatively in agreement with the evidence against the short-term only harvesting. Since long wave cycles (> 6 months) need to be controlled in time-series analyses to avoid seasonal confounding, the extent of harvesting beyond 6 months periodicity is not possible in time-series study design. Also, influenza epidemics can possibly confound the PM-mortality associations in the 1 to 3 month periodicity ranges. Therefore, interpreting PM risk estimates in these "intermediate" time scale also requires cautions. In contrast to Zanobetti, Schwartz and Zeger et al. studies, Smith et al. and Murray and Nelson studies suggest that the frail population is very small and its lifetime short, such that PM or any external stress cannot have more than a few days of life-shortening impacts. This may be an inherent limitation of the model itself. Thus, there appears to be consistency in results within the similar models but not across different types of models. Clearly, more research is needed in this area both in terms of development of conceptual framework that can be tested with real data, and applications of these models to more data sets. However, at least in the models that extend the common time-series modeling, there appears to be no strong evidence to suggest that PM is shortening life by a few days.

8.4.9.2 Life-Shortening Estimates Based on Semi-Individual Cohort Study Results

Brunekreef (1997) reviewed the available evidence of the mortality effects of long-term exposure to PM air pollution and, using life table methods, derived an estimate of the reduction in life expectancy implied by those effect estimates. Based on the results of Pope et al. (1995) and Dockery et al. (1993), a relative risk of 1.1 per 10 $\mu g/m^3$ exposure over 15 years was assumed for the effect of PM air pollution on men 25-75 years of age. A 1992 life table for men in the Netherlands was developed for 10 successive five-year categories that make up the 25-75 year old age range. Life expectancy of a 25 year old was then calculated for this base case and compared with the calculated life expectancy for the PM-exposed case, in which the death rates were increased in each age group by a factor of 1.1. A difference of 1.11 years was found

between the "exposed" and "clean air" cohorts' overall life expectancy at age 25. Looked at another way, this implies that the expectation of the lifespan for persons who actually died from air pollution was reduced by more than 10 years, because they represent a small percentage of the entire cohort population. A similar calculation by the authors for the 1969-71 life table for U.S. white males yielded an even larger reduction of 1.31 years for the entire population's life expectancy at age 25. Thus, these calculations imply that relatively small differences in long-term exposure to ambient PM can substantially affects on life expectancy.

8.4.9.3 Potential Effects of Infant Mortality on Life-Shortening Estimates

Deaths among children can logically have the greatest influence on a population's overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible long-term air pollution exposure effects on the population aged < 25 years. As discussed above, some of the older cross-sectional studies and the more recent studies by Bobak and Leon (1992), Woodruff et al. (1997), Bobak and Leon (1999), and Loomis et al. (1999) suggest that infants may be among the sub-populations notably affected by long-term PM exposure. Thus, although it is difficult to quantify, any premature mortality that does occur among children due to long-term PM exposure (as suggested by these new studies) would significantly increase the overall population life shortening over and above that estimated by Brunekreef (1997) for long-term PM exposure of adults aged 25 years and older.

8.5 SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES

The most important types of additions to the database beyond that assessed in the 1996 PM AQCD, as evaluated above in this chapter, are:

(1) New multi-city studies on a variety of endpoints which provide more precise estimates of the average PM effect sizes than most smaller-scale individual city studies;

(2) More studies of various health endpoints using ambient PM_{10} and/or closely related mass concentration indices (e.g., PM_{13} and PM_{7}), which substantially lessen the need to rely on non-gravimetric indices (e.g., BS or CoH);

(3) New studies evaluating relationships of a variety of health endpoints to the ambient PM coarse fraction ($PM_{10-2.5}$), the ambient fine-particle fraction ($PM_{2.5}$), and even ambient ultrafine particles measures ($PM_{0.1}$ and smaller), using direct mass measurements and/or estimated from site-specific calibrations;

(4) A few new studies in which the relationship of some health endpoints to ambient particle number concentrations were evaluated;

(5) Many new studies which evaluated the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants in the model;

(6) Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures including PM components, based on empirical combinations (e.g., factor analysis or source profiles;

(7) Numerous new studies of cardiovascular endpoints, with particular emphasis on assessment of cardiovascular risk factors as well as symptoms;

(8) Additional new studies on asthma and other respiratory conditions potentially exacerbated by PM exposure;

(9) New analyses of lung cancer associations with long-term exposures to ambient PM;

(10) New studies of infants and children as a potentially susceptible population.

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) There appears to be some spatial heterogeneity in 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 apparent 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.

(4) A smaller body of evidence appears to support an association between short-term ambient thoracic coarse fraction ($PM_{10-2.5}$) exposures (inferred from stationary air monitor measures) and short-term health effects in epidemiology studies. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may be a contributory cause of adverse health effects in some locations. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, but several of the locations where significant $PM_{10-2.5}$ effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend to be in drier climates and may have contributions to observed effects due to higher levels of organic particles from biogenic processes (endotoxins, molds, etc.) during warm months. Other studies suggest that particles of crustal origin are generally unlikely to exert notable health effects under most ambient exposure conditions, (however, see Item 14, below). Also, in some western U.S. cities where $PM_{10-2.5}$ is a large part of PM_{10}, the relationship between

hospital admissions and PM_{10} may be an indicator of response to coarse thoracic particles from wood burning.

(5) Long-term PM exposure durations, on the order of months to years, as well as on the order of a few days, are statistically associated with serious human health effects (indexed by mortality, hospital admissions/medical visits, etc.). More chronic PM exposures, on the order of years or decades, appear to be associated with life shortening well beyond that accounted for by the simple accumulation of the more acute effects of short-term PM exposures (on the order of a few days). Some uncertainties remain regarding the magnitude of and mechanisms underlying chronic health effects of long-term PM exposures and the relationship between chronic exposure and acute responses to short-term exposure.

(6) Recent investigations of the public health implications of such chronic PM exposure-mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne PM of ambient origin can have substantial effects on life expectancy. For example, a calculation for the 1969-71 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25. Also, new evidence of associations of PM exposure with infant mortality (Bobak and Leon, 1992, 1999; Woodruff et al., 1997; Loomis et al., 1999) and/or intrauterine growth retardation (Dejmek et al., 1999) and consequent increase risk for many serious health conditions associated with low birth weight, if further substantiated, would imply that life shortening in the entire population from long-term PM exposure could well be significantly larger than that estimated by Brunekreef (1997).

(7) Considerable coherence exists among effect size estimates for ambient PM health effects. For example, results derived from several multi-city studies, based on pooled analyses of data combined across multiple cities (thought to yield the most precise estimates of mean effect size), show the percent excess total (non-accidental) deaths estimated per 50 $\mu g/m^3$ increase in 24-h PM_{10} to be: 1.4% in the 90 largest U.S. cities with the estimate for the Northeast being the largest (approximately twice the nationwide estimate); 3.4% in 10 large U.S. cities; 3.6% in the 8 largest Canadian cities;

and 3.0% in western European cities (using PM_{10} = TSP*0.55). These combined estimates are consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD. These and excess risk estimates from many other individual-city studies, generally falling in the range of ca. 1.5 to 8.0% per 50 $\mu g/m^3$ 24-h PM_{10} increment, also comport well with numerous new studies confirming increased cause-specific cardiovascular- and respiratory-related mortality. They are also coherent with larger effect sizes reported for cardiovascular and respiratory hospital admissions and visits, as would be expected for these morbidity endpoints versus those for PM_{10}-related mortality.

(8) Several independent panel studies (but not all) that evaluated temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects provide generally consistent indications of decreased heart rate variability (HRV) being associated with ambient PM exposure (decreased HRV being an indicator of increased risk for serious cardiovascular outcomes, e.g., heart attacks). Other studies point toward changes in blood characteristics (e.g., C-reactive protein levels) related to increased risk of ischemic heart disease also being associated with ambient PM exposures. However, these heart rhythm and blood characteristics findings should currently be viewed as providing only limited or preliminary support for PM-related cardiovascular effects.

(9) Notable new evidence now exists which substantiates positive associations between ambient PM concentrations and increased respiratory-related hospital admissions, emergency department, and other medical visits, particularly in relation to PM_{10} levels. Of much interest are new findings tending to implicate not only fine particle components but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of asthma conditions. Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure. Also of particular interest are reanalyses or extensions of earlier prospective cohort studies of long-term ambient PM exposure effects which demonstrate substantial evidence for association of increased lung cancer risk with such PM exposures, especially exposure to fine PM or its subcomponents.

(10) One major methodological issue affecting epidemiology studies of both short-term and long-term PM exposure effects is that ambient PM of varying size ranges is typically found in association with other air pollutants, including gaseous criteria pollutants (e.g, O_3, NO_2, SO_2, CO), air toxics, and/or bioaerosols. Available statistical methods for assessing potential confounding arising from these associations may not yet be fully adequate. The inclusion of multiple pollutants often produces statistically unstable estimates. Omission of other pollutants may incorrectly attribute their independent effects to PM. Second-stage regression methods may have certain pitfalls that have not yet been fully evaluated. Much progress in sorting out relative contributions of ambient PM components versus other co-pollutants is nevertheless being made and, overall, tends to substantiate that observed PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants. However, the statistical association of health effects with PM acting alone or with other pollutants should not be taken as an indicator of a lack of effect of the other pollutants. Indeed, the effects of the other pollutants may at times be greater or less than the effects attributed to PM and may vary from place to place or from time to time.

(11) It is possible that differences in observed health effects will be found to depend on site-specific differences in chemical and physical composition characteristics of ambient particles and on factors affecting exposure (such as air conditioning) as well as on differences in PM mass concentration. For example, the Utah Valley study (Dockery et al., 1999; Pope et al., 1991, 1999b) showed that PM_{10} particles, known to be richer in metals during exposure periods while the steel mill was operating, were more highly associated with adverse health effects than was PM_{10} during the PM exposure reduction while the steel mill was closed. In contrast, PM_{10} or $PM_{2.5}$ was relatively higher in crustal particles during windblown dust episodes in Spokane and in three central Utah sites than at other times, but was not associated with higher total mortality. These differences require more research that may become more feasible as the $PM_{2.5}$ sampling network produces air quality data related to speciated samples.

(12) The above reasons suggest it is inadvisable to pool epidemiology studies at different locations, different time periods, with different population sub-groups, or different health endpoints, without assessing potential causes and the consequences of these

differences. Published multi-city analyses using common data bases, measurement devices, analytical strategies, and extensive independent external review, as carried out in the APHEA and NMMAPS studies are likely to be useful. Pooled analyses of more diverse collections of independent studies of different cities, using varying methodology and/or data quality or representativeness, are likely less credible and should not, in general, be used without careful assessment of their underlying scientific comparability.

(13) It may be possible that different PM size components or particles with different composition or sources produce effects by different mechanisms manifested at different lags, or that different preexisting conditions may lead to different delays between exposure and effect. Thus, although maximum effect sizes for PM effects have often been reported for 0-1 day lags, evidence is also beginning to suggest that more consideration should be given to lags of several days. Also, if it is considered that all health effects occurring at different lag days are all real effects, so that the risks for each lag day should be additive, then higher overall risks may exist that are higher than implied by maximum estimates for any particular single or two-day lags. In that case, multi-day averages or distributed lag models should be used.

(14) Certain classes of ambient particles may be distinctly less toxic than others and may not exert human health effects at typical ambient exposure concentrations or only under special circumstances. Coarse thoracic particles of crustal origin, for example, may be relatively non-toxic under most circumstances compared to those of combustion origin such as wood burning. However, crustal particles may be sufficiently toxic to cause human health effects under some conditions; resuspended crustal particles, for example, may carry toxic trace elements and other components from previously deposited fine PM, e.g., metals from smelters (Phoenix) or steel mills (Steubenville, Utah Valley), PAH's from automobile exhaust, or pesticides from administration to agricultural lands. Likewise, fine particles from different sources have different effect sizes. More research is needed to identify conditions under which one or another class of particles may cause little or no adverse health effects, as well as conditions under which particles may cause notable effects.

(15) Certain epidemiology evidence suggests that reducing ambient PM_{10} concentrations may reduce a variety of health effects on a time scale from a few days to a few months. This has been found in epidemiology studies of "natural experiments" such as in the Utah Valley, and by supporting toxicology studies using the particles from ambient community sampling filters from the Utah Valley. Recent studies in Germany and in the Czech Republic also tend to support a hypothesis that reductions in air pollution are associated with reductions in the incidence of adverse health effects.

(16) Studies that combine the features of cross-sectional and cohort studies provide the best evidence for chronic effects of PM exposure. Gauderman et al. (2000; 2002) have found significant decreases in lung function growth related to PM_{10} levels using these techniques.

(17) Adverse health effects in children are emerging as a more important area of concern than in the 1996 PM AQCD. Unfortunately, relatively little is known about the relationship of PM to the most serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in older children).

(18) Little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue because childhood illness or death may cost a very large number of productive life-years. Lastly, new epidemiologic studies of ambient PM associations with increased non-hospital medical visits (physician visits) and asthma effects suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed by mortality and/or hospital admissions/visits.

REFERENCES

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995b) Estimating fine particulates less that 2.5 microns in aerodynamic diameter ($PM_{2.5}$) from airport visibility data in California. J. Exposure Anal. Environ. Epidemiol. 5: 161-180.

Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am. J. Respir. Crit. Care Med. 158: 289-298.

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. C.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1997) Lung function and long term exposure to air pollutants in Switzerland. Am. J. Respir. Crit. Care Med. 155: 122-129.

Agócs, M. M.; White, M. C.; Ursicz, G.; Olson, D. R.; Vámos, A. (1997) A longitudinal study of ambient air pollutants and the lung peak expiratory flow rates among asthmatic children in Hungary. Int. J. Epidemiol. 26: 1272-1280.

Alberdi Odriozola, J. C.; Díaz Jiménez, J.; Montero Rubio, J. C.; Mirón Pérez, I. J.; Pajares Ortíz, M. S.; Ribera Rodrigues, P. (1998) Air pollution and mortality in Madrid, Spain: a time-series analysis. Int. Arch. Occup. Environ. Health 71: 543-549.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Strachan, D. P. (1996) Air pollution and daily mortality in London: 1987-92. Br. Med. J. 312: 665-669.

Anderson, H. R.; Spix, C.; Medina, S.; Schouten, J. P.; Castellsague, J.; Rossi, G.; Zmirou, D.; Touloumi, G.; Wojtyniak, B.; Ponka, A.; Bacharova, L.; Schwartz, J.; Katsouyanni, K. (1997) Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur. Respir. J. 10: 1064-1071.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Emberlin, J.; Strachen, D. P. (1998) Air pollution, pollens, and daily admissions for asthma in London 1987-92. Thorax 53: 842-848.

Anderson, H. R.; Bremner, S. A.; Atkinson, R. W.; Harrison, R. M.; Walters, S. (2001) Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup. Environ. Med. 58: 504-510.

Archer, V. E. (1990) Air pollution and fatal lung disease in three Utah counties. Arch. Environ. Health 45: 325-334.

Atkinson, R. W.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Bremner, S. A.; Ponce de Leon, A. (1999a) 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.; Bremner, S. A.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Ponce de Leon, A. (1999b) 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.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.; Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2001) Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Am. J. Respir. Crit. Care Med. 164: 1860-1866.

Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.; Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2003) Acute effects of particulate air pollution on respiratory admissions. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 81-84. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Ayres, J. G. (2002) Chronic effects of air pollution [editorial]. Occup. Environ. Med. 59: 147-148.

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.

Bateson, T. F.; Schwartz, J. (2001) Selection bias and confounding in case-crossover analyses of environmental time-series data. Epidemiology 12: 654-661.

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.

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.; Goldberg, M. S. (2003) Size-fractionated particulate mass and daily mortality in eight Canadian cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 85-90. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997a) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; 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.

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.

Carroll, R. J.; Ruppert, D.; Stefanski, L. A. (1995) Measurement error in nonlinear models. London, United Kingdom: Chapman & Hall. (Cox, D. R.; Hinkley, D. V.; Keiding, N.; Reid, N.; Rubin, D. B.; Silverman, B. W., eds. Monographs on statistics and applied probability: v. 63).

Carrothers, T. J.; Evans, J. S. (2000) Assessing the impact of differential measurement error on estimates of fine particle mortality. J. Air Waste Manage. Assoc. 50: 65-74.

Cassino, C.; Ito, K.; Bader, I.; Ciotoli, C.; Thurston, G.; Reibman, J. (1999) Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. Am. J. Respir. Crit. Care Med. 159: 1773-1779.

Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and mortality. In: Phalen, R. F., ed. Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 61-72.

Chay, K. Y.; Greenstone, M. (2001a) Air quality, infant mortality, and the Clean Air Act of 1970. Berkeley, CA: University of California, Berkeley, Department of Economics. Available: http://elsa.berkeley.edu/users/kenchay/ [30 May, 2003].

Chay, K. Y.; Greenstone, M. (2001b) 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/ [30 May, 2003].

Checkoway, H.; Levy, D.; Sheppard, L.; Kaufman, J.; Koenig, J.; Siscovick, D. (2000) A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. Cambridge, MA: Health Effects Institute; research report no. 99. Available: http://www.healtheffects.org/pubs-recent.htm [19 March, 2001].

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.

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. Seattle, WA: University of Washington, National Research Center for Statistics and the Environment; NRCSE technical report series, NRCSE-TRS no. 040. Available: http://www.nrcse.washington.edu/research/reports.html [30 May, 2003].

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.

Cook, J. R.; Stefanski, L. A. (1994) Simulation-extrapolation estimation in parametric measurement error models. J. Am. Stat. Assoc. 89: 1314-1328.

Coull, B. A.; Schwartz, J.; Wand, M. P. (2001) Respiratory health and air pollution: additive mixed model analyses. Biostatistics 2: 337-349.

Coutant, R. W. (1977) Effect of environmental variables on collection of atmospheric sulfate. Environ. Sci. Technol. 11: 873-878.

Creason, J.; Neas, L.; Walsh, D.; Williams, R.; Sheldon, L.; Liao, D.; Shy, C. (2001) Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 PM study. J. Exposure Anal. Environ. Epidemiol. 11: 116-122.

Cropper, M. L.; Simon, N. B.; Alberini, A.; Arora, S.; Sharma, P. K. (1997) The health benefits of air pollution control in Delhi. Am. J. Agric. Econ. 79: 1625-1629.

Cuijpers, C. E. J.; Swaen, G. M. H.; Wesseling, G.; Wouters, E. F. M. (1994) Acute respiratory effects of summer smog in primary school children. Toxicol. Lett. 72: 227-235.

Dab, W.; Medina, S.; Quénel, P.; Le Moullec, Y.; Le Tertre, A.; Thelot, B.; Monteil, C.; Lameloise, P.; Pirard, P.; Momas, I.; Ferry, R.; Festy, B. (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S42-S46.

Damiá, A. D.; Fabregas, M. L.; Tordera, M. P.; Torrero, L. C. (1999) Effects of air pollution and weather conditions on asthma exacerbation. Respiration 66: 52-58.

Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am. J. Epidemiol. 152: 397-406.

Daniels, M. J.; Lee, Y.-D.; Kaiser, M. (2001) Assessing sources of variability in measurement of ambient particulate matter. Environmetrics 12: 547-558.

Dejmek, J.; Selevan, S. G.; 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.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; McLaren, C. E. (2002) Association of asthma symptoms with peak particulate air pollution and effect modification by anti-inflammatory medication use. Environ. Health Perspect. 110: A607-A617.

Desqueyroux, H.; Pujet, J.-C.; Prosper, M.; Squinazi, F.; Momas, I. (2002) Short-term effects of low-level air pollution on respiratory health of adults suffering from moderate to severe asthma. Environ. Res. A 89: 29-37.

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. (1981) Personal exposure to respirable particulates and sulfates. J. Air Pollut. Control Assoc. 31: 153-159.

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.

Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S. L.; Samet, J. M. (2003) Shape of the exposure-response relation and mortality displacement in the NMMAPS database. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 91-96. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Fairley, D. (2003) Mortality and air pollution for Santa Clara County, California, 1989-1996. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 97-106. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Fung, K. Y.; Krewski, D. (1999) On measurement error adjustment methods in Poisson regression. Environmetrics 10: 213-224.

Fusco, D.; Forastiere, F.; Michelozzi, P.; Spadea, T.; Ostro, B.; Arca, M.; Perucci, C. A. (2001) Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur. Respir. J. 17: 1143-1150.

Gamble, J. L. (1998) Effects of ambient air pollution on daily mortality: a time series analysis of Dallas, Texas, 1990-1994. Presented at: 91st annual meeting and exhibition of the Air & Waste Management Association; June; San Diego, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 98-MP26.03.

Garcia-Aymerich, J.; Tobias, A.; Anto, J. M.; Sunyer, J. (2000) Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis. J. Epidemiol. Community Health 54: 73-74.

Garty, B. Z.; Kosman, E.; Ganor, E.; Berger, V.; Garty, L.; Wietzen, T.; Waisman, Y.; Mimouni, M.; Waisel, Y. (1998) Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. Ann. Allergy Asthma Immunol. 81: 563-570.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Gauderman, W. J.; Gilliland, G. F.; Vora, H.; Avol, E.; Stram, D.; McConnell, R.; Thomas, D.; Lurmann, F.; Margolis, H. G.; Rappaport, E. B.; Berhane, K.; Peters, J. M. (2002) Association between air pollution and lung function growth in southern California children: results from a second cohort. Am. J. Respir. Crit. Care Med. 166: 76-84.

Gauvin, S.; Zmirou, D.; Pin, I.; Quentin, J.; Balducci, F.; Boudet, C.; Poizeau, D.; Brambilla, C. (1999) Short-term effect of exposure to suspended particulate matter (PM10) on the respiratory function of urban asthmatic and control adults. J. Environ. Med. 1: 71-79.

Gehring, U.; Cyrys, J.; Sedlmeir, G.; Brunekreef, B.; Bellander, T.; Fischer, P.; Bauer, C. P.; Reinhardt, D.; Wichmann, H. E.; Heinrich, J. (2002) Traffic-related air pollution and respiratory health during the first 2 yrs. of life. Eur. Respir. J. 19: 690-698.

Gherghinova, M.; Kostyanve, S.; Ivanova, M. (1989) Theoretic values of body plethysmography indices in healthy children between 7 and 14 years of age. Pediatria 28: 52-58.

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.

Gold, D. R.; Schwartz, J.; Litonjua, A.; Verrier, R.; Zanobetti, A. (2003) Ambient pollution and reduced heart rate variability. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 107-112. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Goldberg, M. S.; Burnett, R. T. (2003) Revised analysis of the Montreal time-series study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 113-132. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Goldberg, M. S.; Burnett, R. T.; Valois, M.-F.; Flegel, K.; Bailar, J. C., III; Brook, J.; Vincent, R.; Radon, K. (2003) Associations between ambient air pollution and daily mortality among persons with congestive heart failure. Environ. Res. 91: 8-20.

Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. Environ. Health Perspect. 104: 290-297.

Gouveia, N.; Fletcher, T. (2000) Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occup. Environ. Med. 57: 477-483.

Grievink, L.; Van der Zee, S. C.; Hoek, G.; Boezen, H. M.; Van't Veer, P.; Brunekreef, B. (1999) Modulation of the acute respiratory effects of winter air pollution by serum and dietary antioxidants: a panel study. Eur. Respir. J. 13: 1439-1446.

Güntzel, O.; Bollag, U.; Helfenstein, U. (1996) Asthma and exacerbation of chronic bronchitis: sentinel and environmental data in a time series analysis. Zentralbl. Hyg. Umweltmed. 198: 383-393.

Guo, Y. L.; Lin, Y.-C.; Sung, F.-C.; Huang, S.-L.; Ko, Y.-C.; Lai, J.-S.; Su, H.-J.; Shaw, C.-K.; Lin, R.-S.; Dockery, D. W. (1999) Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ. Health Perspect. 107: 1001-1006.

Gwynn, R. C.; Thurston, G. D. (2001) The burden of air pollution: impacts among racial minorities. Environ. Health Perspect. 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.

Health Effects Institute. (2002) Reanalysis of National Morbidity, Mortality, and Air Pollution Study (NMMAPS) [letter with attachments]. Boston, MA: May 30.

Health Effects Institute. (2003a) Revised analyses of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), part II. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 9-72. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Health Effects Institute. (2003b) Commentary on revised analyses of selected studies. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 255-290. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. Arch. Environ. Health 49: 170-174.

Heinrich, J.; Hoelscher, B.; Wjst, M.; Ritz, B.; Cyrys, J.; Wichmann, H.-E. (1999) Respiratory diseases and allergies in two polluted areas in East Germany. Environ. Health Perspect. 107: 53-62.

Heinrich, J.; Hoelscher, B.; Wichmann, H. E. (2000) Decline of ambient air pollution and respiratory symptoms in children. Am. J. Respir. Crit. Care Med. 161: 1930-1936.

Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Pitz, M.; Cyrys, J.; Wjst, M.; Neas, L.; Wichmann, H.-E. (2002) Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 13: 394-401.

Henderson, B. E.; Gordon, R. J.; Menck, H.; SooHoo, J.; Martin, S. P.; Pike, M. C. (1975) Lung cancer and air pollution in southcentral Los Angeles County. Am. J. Epidemiol. 101: 477-488.

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. (2003) Daily mortality and air pollution in The Netherlands. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 133-142. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Horak, F., Jr.; Studnicka, M.; Gartner, C.; Spengler, J. D.; Tauber, E.; Urbanek, R.; Veiter, A.; Frischer, T. (2002) Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. Eur. Respir. J. 19: 838-845.

Howel, D.; Darnell, R.; Pless-Mulloli, T. (2001) Children's respiratory health and daily particulate levels in 10 nonurban communities. Environ. Res. 87: 1-9.

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.

Ito, K. (2003) Associations of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 143-156. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 735-745.

Ito, K.; Thurston, G. D.; Nádas, A.; Lippmann, M. (2001) Monitor-to-monitor temporal correlation of air pollution and weather variables in the North-Central U.S. J. Exposure Anal. Environ. Epidemiol. 11: 21-32.

Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California, 1983-1992. Environ. Health Perspect. 105: 980-985.

Jalaludin, B. B.; Chey, T.; O'Toole, B. I.; Smith, W. T.; Capon, A. G.; Leeder, S. R. (2000) Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. Int. J. Epidemiol. 29: 549-557.

Jamason, P. F.; Kalkstein, L. S.; Gergen, P. J. (1997) A synoptic evaluation of asthma hospital admissions in New York City. Am. J. Respir. Crit. Care Med. 156: 1781-1788.

Janssen, N. A. H.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as modifiers of the effect of PM_{10} on hospital admissions for heart and lung disease. Environ. Health Perspect. 110: 43-49.

Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpialek, Z. (1990) A case-control study of lung cancer with special erence 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.

Just, J.; Ségala, C.; Sahraoui, F.; Priol, G.; Grimfeld, A.; Neukirch, F. (2002) Short-term health effects of particulate and photochemical air pollution in asthmatic children. Eur. Respir. J. 20: 899-906.

Katsouyanni, K.; Touloumi, G. (1998) Causes of regional differences in air pollution effects are being studied further [letter]. Br. Med. J. 316: 1982.

Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990) Air pollution and cause specific mortality in Athens. J. Epidemiol. Community Health 44: 321-324.

Katsouyanni, K.; Schwartz, J.; Spix, C.; Touloumi, G.; Zmirou, D.; Zanobetti, A.; Wojtyniak, B.; Vonk, J. M.; Tobias, A.; Pönkä, A.; Medina, S.; Bachárová, L.; Andersen, H. R. (1996) Short term effects of air pollution on health: a European approach using epidemiology time series data: the APHEA protocol. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S12-S18.

Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.; Sunyer, J.; Bachárová, L.; Schouten, J. P.; Pönkä, A.; Anderson, H. R. (1997) Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br. Med. J. 314: 1658-1663.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Gryparis, A.; Le Tertre, A.; Monopolis, Y.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12: 521-531.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2003) Sensitivity analysis of various models of short-term effects of ambient particles on total mortality in 29 cities in APHEA2. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 157-164. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Keatinge, W. R.; Donaldson, G. C. (2001) Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. Environ. Res. A 86: 209-216.

Keles, N.; Ilicali, Ö. C.; Deger, K. (1999) Impact of air pollution on prevalence of rhinitis in Istanbul. Arch. Environ. Health 54: 48-51.

Kelsall, J. E.; Samet, J. M.; Zeger, S. L.; Xu, J. (1997) Air pollution and mortality in Philadelphia, 1974-1988. Am. J. Epidemiol. 146: 750-762.

Kinney, P. L.; Aggarwal, M.; Northridge, M. E.; Janssen, N. A. H.; Shepard, P. (2000) Airborne concentrations of $PM_{2.5}$ and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. Environ. Health Perspect. 108: 213-218.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling—interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. (2003) Replication of reanalysis of Harvard Six-City mortality study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 165-172. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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) erence 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.

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 56: 773-779.

Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.; Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2003) Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 173-176. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Levy, D.; Sheppard, L.; Checkoway, H.; Kaufman, J.; Lumley, T.; Koenig, J.; Siscovick, D. (2001a) A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12: 193-199.

Levy, D.; Lumley, T.; Sheppard, L.; Kaufman, J.; Checkoway, H. (2001b) Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 12: 186-192.

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.; Morris, S. C. (2002) Temporal and spacial relationships between age-specific mortality and ambient air quality in the United States: preliminary results for counties, 1960-97. Occup. Environ. Med. 59: 156-174.
Lipfert, F. W.; Wyzga, R. E. (1996) The effects of exposure error on environmental epidemiology. In: Phalen, R. F.; Mannix, R. C.; Tonini, M. C., eds. The second colloquium on particulate air pollution & human mortality & morbidity: report to the California Air Resources Board; May; Park City, UT. Sacramento, CA: State of California, Air Resources Board; pp. 4-295--4-302; ARB contract no. 95-323. (University of California Air Pollution Health Effects Laboratory report no. 96-02). Available: http://www.arb.ca.gov/research/abstracts/95-323.htm#Ch95-323 (24 September 2002).
Lipfert, F. W.; Wyzga, R. E. (1997) Air pollution and mortality: the implications of uncertainties in regression modeling and exposure measurement. J. Air Waste Manage. Assoc. 47: 517-523.
Lipfert, F. W.; 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.; Levy, D. (2000) Bias in the case-crossover design: implications for studies of air pollution. Environmetrics 11: 689-704.
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.
Magari, S. R.; Hauser, R.; Schwartz, J.; Williams, P. L.; Smith, T. J.; Christiani, D. C. (2001) Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104: 986-991.
Magari, S. R.; Schwartz, J.; Williams, P. L.; Hauser, R.; Smith, T. J.; Christiani, D. C. (2002) The association between personal measurements of environmental exposure to particulates and heart rate variability. Epidemiology 13: 305-310.
Mage, D.; Wilson, W.; Hasselblad, V.; Grant, L. (1999) Assessment of human exposure to ambient particulate matter. J. Air Waste Manage. Assoc. 49: 174-185.
Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.
Mar, T. F.; Norris, G. A.; Larson, T. V.; Wilson, W. E.; Koenig, J. Q. (2003) Air pollution and cardiovascular mortality in Phoenix, 1995-1997. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 177-182. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Marcus, A. H.; Chapman, R. (1998) Estimating the health effects of fine particles from epidemiology studies: how serious are problems of measurement error, correlation, and confounding? In: Chow, J.; Koutrakis, P., eds. $PM_{2.5}$: a fine particle standard. Volume II: proceedings of an international specialty conference.; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 899-919.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.; Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern California children with asthma. Environ. Health Perspect. 107: 757-760.

McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Islam, T.; Gauderman, W. J.; Avol, E.; Margolis, H. G.; Peters, J. M. (2002) Asthma in exercising children exposed to ozone: a cohort study. Lancet 359: 386-391.

McDonnell, W. F.; Nishino-Ishikawa, N.; Petersen, F. F.; Chen, L. H.; Abbey, D. E. (2000) Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J. Exposure Anal. Environ. Epidemiol. 10: 427-436.

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.

McMahon, B.; Pugh, T. F. (1970) Epidemiology: principles and methods. Boston, MA: Little, Brown and Company.

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.

Metzger, K. B.; Tolbert, P. E.; Klein, M.; Peel, J. L.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2003) Ambient air pollution and cardiovascular emergency department visits in Atlanta, Georgia, 1993-2000. Epidemiology: in press.

Michelozzi, P.; Forastiere, F.; Fusco, D.; Perucci, C. A.; Ostro, B.; Ancona, C.; Pallotti, G. (1998) Air pollution and daily mortality in Rome, Italy. Occup. Environ. Med. 55: 605-610.

Miller, J. P.; Perry, H. M., Jr.; Rossiter, J. E.; Baty, J. D.; Carmody, S. E.; Sambhi, M. P. (1994) Regional differences in mortality during 15-year follow-up of 11,936 hypertensive veterans. Hypertension 23: 431-438.

Mills, P. K.; Abbey, D.; Beeson, W. L.; Petersen, F. (1991) Ambient air pollution and cancer in California Seventh-day Adventists. Arch. Environ. Health 46: 271-280.

Monn, C. (2001) Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmos. Environ. 35: 1-32.

Monn, Ch.; Carabias, V.; Junker, M.; Waeber, R.; Karrer, M.; Wanner, H. U. (1997) Small-scale spatial variability of particulate matter <10 μm (PM_{10}) and nitrogen dioxide. Atmos. Environ. 31: 2243-2247.

Moolgavkar, S. H. (2000a) Air Pollution and Mortality in Three U.S. Counties. Environ. Health Perspect. 108: 777-784.

Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.

Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.

Moolgavkar, S. H. (2003) Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 183-198. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Moolgavkar, S. H.; Luebeck, E. G. (1996) A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7: 420-428.

Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology 8: 364-370.

Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions for chronic respiratory disease in King County, Washington. In: Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 157-171.

Morgan, G.; Corbett, S.; Wlodarczyk, J.; Lewis, P. (1998) Air pollution and daily mortality in Sydney, Australia, 1989 through 1993. Am. J. Public Health 88: 759-764.

Morris, R. D. (2001) Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. Environ. Health Perspect. 109(suppl. 4): 495-500.

Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.

Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am. J. Public Health 85: 1361-1365.

Mortimer, K. M.; Neas, L. M.; Dockery, D. W.; Redline, S.; Tager, I. B. (2002) The effect of air pollution on inner-city children with asthma. Eur. Respir. J. 19: 699-705.

Murray, C. J.; Nelson, C. R. (2000) State-space modeling of the relationship between air quality and mortality. J. Air Waste Manage. Assoc. 50: 1075-1080.

Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999) Healthy women's PEF variations with ambient summer concentrations of PM_{10}, $PM_{2.5}$, SO_4^{2-}, H^+, and O_3. Am. J. Respir. Crit. Care Med. 160: 117-125.

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.

Navidi, W. (1998) Bidirectional case-crossover designs for exposures with time trends. Biometrics 54: 596-605.

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.

Nemmar, A.; Hoet, P. 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.

Neukirch, F.; Ségala, C.; Le Moullec, Y.; Korobaeff, M.; Aubier, M. (1998) Short-term effects of low-level winter pollution on respiratory health of asthmatic adults. Arch. Environ. Health 53: 320-328.

Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.

Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and stagnant air. Thorax 55: 466-470.

Nyberg, F.; Gustavsson, P.; Järup, L.; Bellander, T.; Berglind, N.; Jakobsson, R.; Pershagen, G. (2000) Urban air pollution and lung cancer in Stockholm. Epidemiology 11: 487-495.

Ostro, B. (1995) Fine particulate air pollution and mortality in two Southern California counties. Environ. Res. 70: 98-104.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.

Ostro, B.; Chestnut, L.; Vichit-Vadakan, N.; Laixuthai, A. (1998) The impact of fine particulate matter in Bangkok, Thailand. In: Chow, J.; Koutrakis, P., eds. PM2.5: a fine particle standard. Volume II: proceedings of an international specialty conference; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 939-949. (A&WMA publication VIP-81).

Ostro, B. D.; Hurley, S.; Lipsett, M. J. (1999a) Air pollution and daily mortality in the Coachella Valley, California: a study of PM_{10} dominated by coarse particles. Environ. Res. 81: 231-238.

Ostro, B. D.; Eskeland, G. S.; Sanchez, J. M.; Feyzioglu, T. (1999b) Air pollution and health effects: a study of medical visits among children in Santiago, Chile. Environ. Health Perspect. 107: 69-73.

Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, CA: a follow-up study. J. Exposure Anal. Environ. Epidemiol.: 10: 412-419.

Ostro, B.; Lipsett, M.; Mann, J.; Braxtron-Owens, H.; White, M. (2001) Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology 12: 200-208.

Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2003) Coarse particles and daily mortality in Coachella Valley, California. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 199-204. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Osunsanya, T.; Prescott, G.; Seaton, A. (2001) Acute respiratory effects of particles: mass or number? Occup. Environ. Med. 58: 154-159.

Ott, W.; Wallace, L.; Mage, D. (2000) Predicting particulate (PM_{10}) personal exposure distributions using a random component superposition statistical model. J. Air Waste Manage. Assoc. 50: 1390-1406.

Özkaynak, H.; Xue, J.; Zhou, H.; Raizenne, M. (1996) Associations between daily mortality and motor vehicle pollution in Toronto, Canada. Boston, MA: Harvard University School of Public Health, Department of Environmental Health; March 25.

Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. (1995) Short-term effects of air pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. Environ. Res. 69: 31-36.

Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ. Res. 74: 24-33.

Pekkanen, J.; Brunner, E. J.; Anderson, H. R.; Tiittanen, P.; Atkinson, R. W. (2000) Daily concentrations of air pollution and plasma fibrinogen in London. Occup. Environ. Med. 57: 818-822.

Penttinen, P.; Timonen, K. L.; Tiittanen, P.; Mirme, A.; Ruuskanen, J.; Pekkanen, J. (2001) Number concentration and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. Environ. Health Perspect. 109: 319-323.

Pereira, L. A. A.; Loomis, D.; Conceição, G. M. S.; Braga, A. L. F.; Arcas, R. M.; Kishi, H. S.; Singer, J. M.; Böhm, G. M.; Saldiva, P. H. N. (1998) Association between air pollution and intrauterine mortality in São Paulo, Brazil. Environ. Health Perspect. 106: 325-329.

Perry, H. M., Jr.; Schnaper, H. W.; Meyer, G.; Swatzell, R. (1982) Clinical program for screening and treatment of hypertension in veterans. J. Natl. Med. Assoc. 74: 433-444.

Peters, A.; Goldstein, I. F.; Beyer, U.; Franke, K.; Heinrich, J.; Dockery, D. W.; Spengler, J. D.; Wichmann, H.-E. (1996) Acute health effects of exposure to high levels of air pollution in eastern Europe. Am. J. Epidemiol. 144: 570-581.

Peters, A.; Doring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349: 1582-1587.

Peters, A.; 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.; Skorkovsky, J.; Kotesovec, F.; Brynda, J.; Spix, C.; Wichmann, H. E.; Heinrich, J. (2000b) Associations between mortality and air pollution in central Europe. Environ. Health Perspect. 108: 283-287.

Peters, A.; Dockery, D. W.; Muller, J. E.; Mittleman, M. A. (2001a) Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103: 2810-2815.

Peters, A.; Fröhlich, M.; Döring, A.; Immervoll, T.; Wichmann, H.-E.; Hutchinson, W. L.; Pepys, M. B.; Koenig, W. (2001b) Particulate air pollution is associated with an acute phase response in men: results from the MONICA-Augsburg Study. Eur. Heart J. 22: 1198-1204.

Petroeschevsky, A.; Simpson, R. W.; Thalib, L.; Rutherford, S. (2001) Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch. Environ. Health 56: 37-52.

Pike, M. C.; Jing, J. S.; Rosario, I. P.; Henderson, B. E.; Menck, H. R. (1979) Occupation: "explanation" of an apparent air pollution related localized excess of lung cancer in Los Angeles County. In: Breslow, N. E.; Whitemore, A. S., eds. Energy and Health: proceedings of a conference sponsored by Siam Institute for Mathematics and Society; 1978; Alta, Utah. [SIAM-SIMS conference series 6].

Pless-Mulloli, T.; Howel, D.; King, A.; Stone, I.; Merefield, J.; Bessell, J.; Darnell, R. (2000) Living near opencast coal mining sites and children's respiratory health. Occup. Environ. Med. 57: 145-151.

Ponce de Leon, A.; Anderson, H. R.; Bland, J. M.; Strachan, D. P.; Bower, J. (1996) Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S63-S70.

Pönkä, A.; Savela, M.; Virtanen, M. (1998) Mortality and air pollution in Helsinki. Arch. Environ. Health 53: 281-286.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III; Kalkstein, L S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. Environ. Health Perspect. 104: 414-420.

Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM_{10} pollution: a daily time series analysis. Am. Rev. Respir. Dis. 144: 668-674.

Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM10 pollution in Utah valley. Arch. Environ. Health 47: 211-217.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999a) Particulate air pollution and daily mortality on Utah's Wasatch Front. Environ. Health Perspect. 107: 567-573.

Pope, C. A., III; Dockery, D. W.; Kanner, R. E.; Vollegas, G. M.; Schwartz, J. (1999b) Oxygen saturation, pulse rate, and particulate air pollution: a daily time-series panel study. Am. J. Respir. Crit. Care Med. 159: 365-372.

Pope, C. A., III; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas, G. M.; Gold, D. R.; Dockery, D. W. (1999c) Heart rate variability associated with particulate air pollution. Am. Heart J. 138: 890-899.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Prescott, G. J.; Cohen, G. R.; Elton, R. A.; Fowkes, F. G. R.; Agius, R. M. (1998) Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. Occup. Environ. Med. 55: 697-704.

Prescott, 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 PM_{10} pollution in Utah Valley. Environ. Res. 58: 204-219.

Roemer, W. H.; Van Wijnen, J. H . (2001) Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology 12: 649-653.

Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147: 118-124.

Roemer, W.; Hoek, G.; Brunekreef, B.; Haluszka, J.; Kalandidi, A.; Pekkanen, J. (1998) Daily variations in air pollution and respiratory health in a multicentre study: the PEACE project. Eur. Respir. J. 12: 1354-1361.

Roemer, W.; Hoek, G.; Brunekreef, B.; Clench-Aas, J.; Forsberg, B.; Pekkanen, J.; Schutz, A. (2000) PM_{10} elemental composition and acute respiratory health effects in European children (PEACE project). Eur. Respir. J. 15: 553-559.

Romieu, I.; Meneses, F.; Ruiz, S.; Sienra, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am. J. Respir. Crit. Care Med. 154: 300-307.

Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch. Environ. Health 52: 368-376.

Rooney, C.; McMichael, A. J.; Kovats, R. S.; Coleman, M. P. (1998) Excess mortality in England and Wales, and in greater London, during the 1995 heatwave. J. Epidemiol. Community Health 52: 482-486.

Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderon, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy (Copenhagen) 53: 394-401.

Rossi, G.; Vigotti, M. A.; Zanobetti, A.; Repetto, F.; Gianelle, V.; and Schwartz, J. (1999) Air pollution and cause-specific mortality in Milan, Italy, 1980-1989. Arch. Environ. Health 54: 158-164.

Rothman, K. J.; Greenland, S., eds. (1998) Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

Rutherford, S.; Clark, E.; McTainsh, G.; Simpson, R.; Mitchell, C. (1999) Characteristics of rural dust events shown to impact on asthma severity in Brisbane, Australia. Int. J. Biometeorol. 42: 217-225.

Samet, J. M. (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 Toxicol. 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. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000a) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000b) National morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Curriero, F. C.; Coursac, I.; Zeger, S. L. (2000c) Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N. Engl. J. Med. 343: 1742-1749.

Samoli, E.; Schwartz, J.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Bacharova, L.; Anderson, H. R.; Katsouyanni, K. (2001) Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. Environ. Health Perspect. 109: 349-353.

Samoli, E.; Schwartz, J.; Analitis, A.; Petasakis, Y.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Anderson, H. R.; Katsouyanni, K. (2003) Sensitivity analyses of regional differences in short-term effects of air pollution on daily mortality in APHEA cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 205-210. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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. (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. (2003a) Daily deaths associated with air pollution in six US cities and short-term mortality displacement in Boston. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 219-226. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Schwartz, J. (2003b) Airborne particles and daily deaths in 10 US cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 211-218. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
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.
Seaton, A.; Soutar, A.; Crawford, V.; Elton, R.; McNerlan, S.; Cherrie, J.; Watt, M.; Agius, R.; Stout, R. (1999) Particulate air pollution and the blood. Thorax 54: 1027-1032.
Segala, C.; Fauroux, B.; Just, J.; Pascual, L.; Grimfeld, A.; Neukirch, F. (1998) Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. Eur. Respir. J. 11: 677-685.
Sheppard, L. (2003) Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 227-230. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Sheppard, L.; Damian, D. (2000) Estimating short-term PM effects accounting for surrogate exposure measurements from ambient monitors. Environmetrics 11: 675-687.
Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.
Sheppard, L.; Levy, D.; Checkoway, H. (2001) Correcting for the effects of location and atmospheric conditions on air pollution exposures in a case-crossover study. J. Exposure Anal. Environ. Epidemiol. 11: 86-96.

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.; Davis, J. M.; Speckman, P. (1999) Assessing the human health risk of atmospheric particles. In: Environmental Statistics: Analysing Data for Environmental Policy: proceedings of a Novartis Foundation Symposium; May 1998; London, England. New York, NY: Wiley. [Novartis Foundation Symposium 220, pp. 59-79].

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.

Stölzel, M.; Peters, A.; Wichmann, H.-E. (2003) Daily mortality and fine and ultrafine particles in Erfurt, Germany. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 231-240. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur. Respir. J. 13: 266-273.

Timonen, K. L.; Pekkanen, J. (1997) Air pollution and respiratory health among children with asthmatic or cough symptoms. Am. J. Respir. Crit. Care Med. 156: 546-552.

Tobias, A.; Campbell, M. J. (1999) Modelling influenza epidemics in the relation between black smoke and total mortality. A sensitivity analysis. J. Epidemiol. Community Health 53: 583-584.

Tolbert, P. E.; Klein, M.; Metzger, K. B.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2000a) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.

Tolbert, P. E.; Mulholland, J. A.; Maclntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.; Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000b) Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia. Am. J. Epidemiol. 151: 798-810.

Touloumi, G.; Katsouyanni, K.; Zmirou, D.; Schwartz, J.; Spix, C.; Ponce de Leon, A.; Tobias, A.; Quennel, P.; Rabczenko, D.; Bacharova, L.; Bisanti, L.; Vonk, J. M.; Ponka, A. (1997) Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Am. J. Epidemiol. 146: 177-185.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (1999) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Berkeley, CA: Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; report no. LBNL-43583.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

Turnovska, T.; Kostianev, S. (1999) Effects of reduced air pollution on children's pulmonary function. Cent. Eur. J. Public Health 7: 77-79.

U.S. Census Bureau. (1995) American housing survey for the United States in 1993. Washington, DC: U.S. Department of Commerce; current housing reports H150/93. Available: http://www.census.gov/hhes/www/housing/ahs/nationaldata.html [29 April, 2002].

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and PB95-124517.

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

U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants. Research Triangle Park, NC: Office of Research and Development; report nos. EPA/600/AP-93/004aF-cF. 3v. Available from: NTIS, Springfield, VA; PB96-185582, PB96-185590, and PB96-185608. Available online at: www.epa.gov/ncea/ozone.htm.

U.S. Environmental Protection Agency. (2000a) Emissions and air quality data. Washington, DC: Technology Transfer Network. Available: http://www.epa.gov/ttn/naaqs/ozone/areas/ [20 May, 2003].

U.S. Environmental Protection Agency. (2000b) Air quality criteria for carbon monoxide. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available: www.epa.gov/ncea/co/ [2000, October 6].

U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; report no. EPA/600/8-90/057F. Available: http://cfpub.epa.gov/ncea/ [22 May, 2003].

Van Der Zee, S. C.; Hoek, G.; Boezen, H. M.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (1999) Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms. Occup. Environ. Med. 56: 802-813.

Van Der Zee, S. C.; Hoek, G.; Boezen, M. H.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (2000) Acute effects of air pollution on respiratory health of 50-70 yr old adults. Eur. Respir. J. 15: 700-709.

Vasan, R. S.; Larson, M. G.; Leip, E. P.; Kannel, W. B.; Levy, D. (2001) Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 358: 1682-1686.

Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am. J. Respir. Crit. Care Med. 157: 1034-1043.

Vena, J. E. (1982) Air pollution as a risk factor in lung cancer. Am. J. Epidemiol. 116: 42-56.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1967) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA J. Am. Med. Assoc. 202: 1028-1034.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1970) Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA J. Am. Med. Assoc. 213: 1143-1152.

Vigotti, M. A.; Rossi, G.; Bisanti, L.; Zanobetti, A.; Schwartz, J. (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. In: Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S71-S75.

Villeneuve, P. J.; Goldberg, M. S.; Krewski, D.; Burnett, R. T.; Chen, Y. (2002) Fine particulate air pollution and all-cause mortality within the Harvard six-cities study: variations in risk by period of exposure. Ann. Epidemiol. 12: 568-576.

Von Klot, S.; Wölke, G.; Tuch, T.; Heinrich, J.; Dockery, D. W.; Schwartz, J.; Kreyling, W. G.; Wichmann, H. E.; Peters, A. (2002) Increased asthma medication use in association with ambient fine and ultrafine particles. Eur. Respir. J. 20: 691-702.

Wallace, L. (1996) Indoor particles: a review. J. Air Waste Manage. Assoc. 46: 98-126.

Wallace, L. (2000) Real-time monitoring of particles, PAH, and CO in an occupied townhouse. Appl. Occup. Environ. Hyg. 15: 39-47.

Wang, B.; Peng, Z.; Zhang, X.; Xu, Y.; Wang, H.; Allen, G.; Wang, L.; Xu, X. (1999) Particulate matter, sulfur dioxide, and pulmonary function in never-smoking adults in Chongqing, China. Int. J. Occup. Environ. Health 5: 14-19.

Ward, D. J.; Miller, M. R.; Walters, S.; Harrison, R. M.; Ayres, J. G. (2000) Impact of correcting peak flow for nonlinear errors on air pollutant effect estimates from a panel study. Eur. Respir. J. 15: 137-140.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; Research Report no. 98.

Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.

Wilson, W. E.; Mage, D. T.; Grant, L. D. (2000) Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. J. Air Waste Manage. Assoc. 50: 1167-1183.

Wjst, M.; Reitmeir, P.; Dold, S.; Wulff, A.; Nicolai, T.; Von Loeffelholz-Colberg, E. F.; Von Mutius, E. (1993) Road traffic and adverse effects on respiratory health in children. Br. Med. J. 307: 596-600.

Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental carbon. J. Air Pollut. Control Assoc. 33: 746-750.

Wong, 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, T. W.; Lau, T. S.; Yu, T. S.; Neller, A.; Wong, S. L.; Tam, W.; Pang, S. W. (1999a) Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup. Environ. Med. 56: 679-683.

Wong, C. M.; Hu, Z. G.; Lam, T. H.; Hedley, A. J.; Peters, J. (1999b) Effects of ambient air pollution and environmental tobacco smoke on respiratory health of non-smoking women in Hong Kong. Int. J. Epidemiol. 28: 859-864.

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. (2003a) Multicity assessment of mortality displacement within the APHEA2 project. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 249-254. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Zanobetti, A.; Schwartz, J. (2003b) Airborne particles and hospital admissions for heart and lung disease. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 241-248. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Zidek, J. V.; Wong, H.; Le, N. D.; Burnett, R. (1996) Causality, measurement error and multicollinearity in epidemiology. Environmetrics 7: 441-451.

Zmirou, D.; Schwartz, J.; Saez, M.; Zanobetti, A.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Ponce de León, A.; Le Moullec, Y.; Bacharova, L.; Schouten, J.; Pönkä, A.; Katsouyanni, K. (1998) Time-series analysis of air pollution and cause-specific mortality. Epidemiology 9: 495-503.

APPENDIX 8A

SHORT-TERM PM EXPOSURE-MORTALITY STUDIES: SUMMARY TABLE

TABLE 8A-1. SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States			
Samet et al. (2000a,b).* 90 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 15.3 (Honolulu) to 52.0 (Riverside).	Non-accidental total deaths and cause-specific (cardiac, respiratory, and the other remaining) deaths, stratified in three age groups (<65, 65-75, 75+), were examined for their associations with PM_{10}, O_3, SO_2, NO_2, and CO (single, two, and three pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for the pollutants for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled within region. The third stage modeled between-region variation (7 regions). Two alternative assumptions were made regarding the prior distribution: one with possibly substantial heterogeneity and the other with less or no heterogeneity within region. The weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate; (3) socio-demographic variables; (4) urbanization; (5) variables related to measurement error.	The estimated city-specific coefficients were mostly positive at lag 0, 1, and 2 days (estimated overall effect size was largest at lag 1, with the estimated percent excess death rate per 10 $\mu g/m^3$ PM_{10} being about 0.5%). The posterior probabilities that the overall effects are greater than 0 at these lags were 0.99, 1.00, and 0.98, respectively. None of the county-specific variables (effect modifiers) in the second-stage regression significantly explained the heterogeneity of PM_{10} effects across cities. In the 3-stage regression model with the index for 7 geographical regions, the effect of PM_{10} varied somewhat across the 7 regions, with the effect in the Northeast being the greatest. Adding O_3 and other gaseous pollutants did not markedly change the posterior distributions of PM_{10} effects. O_3 effects, as examined by season, were associated with mortality in summer (0.5 percent per 10 ppb increase), but not in all season data (negative in winter).	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 2.3% (0.1, 4.5) for "more heterogeneity" across-city assumption; 2.2% (0.5, 4.0) for "less or no heterogeneity" across cities assumption. The largest PM_{10} effect estimated for 7 U.S. regions was for the Northeast: 4.6% (2.7, 6.5) excess deaths per 50 $\mu g/m^3$ PM_{10} increment.
Dominici et al. (2002). Re-analysis of above study.	Illustration of the issues related to GAM convergence criteria using simulation; and re-analysis of above study using stringent convergence criteria as well as comparable GLM model with natural splines.	The overall estimate was reduced but major findings of the study were not changed. Sensitivity analysis using alternative degrees of freedom for temporal trends and weather terms showed that PM_{10} risk estimates were larger when smaller number of degrees of freedom were used.	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 1.4% (0.9, 1.9) using GAM with stringent convergence criteria and 1.1 (0.5, 1.7) using GLM with natural splines. Northeast still has the largest PM_{10} risk estimate.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Dominici et al. (2000a). +20 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 23.8 $\mu g/m^3$ (San Antonio) to 52.0 $\mu g/m^3$ (Riverside).	Non-accidental total deaths (stratified in three age groups: <65, 65-75, 75+) were examined for their associations with PM_{10} and O_3 (single, 2, and 3 pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for PM_{10} and O_3 for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled as a function of city-specific covariates including mean PM_{10} and O_3 levels, percent poverty, and percent of population with age 65 and over. The prior distribution assumed heterogeneity across cities. To approximate the posterior distribution, a Markov Chain Monte Carlo (MCMC) algorithm with a block Gibbs sampler was implemented. The second stage also considered spatial model, in which RRs in closer cities were assumed to be more correlated.	Lag 1 day PM_{10} concentration positively associated with total mortality in most locations (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).
Daniels et al. (2000).* The largest U.S. 20 cities, 1987-1994.	This study examined the shape of concentration-response curve. Three log-linear GAM regression models were compared: (1) using a linear PM_{10} term; (2) using a natural cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. Covariates included the smoothing function of time, temperature and dewpoint, and day-of-week indicators. These models were fit for each city separately, and for model (1) and (2) the combined estimates across cities were obtained by using inverse variance weighting if there was no heterogeneity across cities, or by using a two-level hierarchical model if there was heterogeneity.	For total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold. For mortality from other causes, however, the curve did not increase until PM_{10} concentrations exceeded 50 $\mu g/m^3$. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models.	
Dominici et al. (2003). Re-analysis of above study.	Re-analysis of above model using GLM/natural splines.	The shapes of concentration-response curves were similar to the original analysis.	

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Klemm et al. (2000). Replication study of the Harvard Six Cities time-series analysis by Schwartz et al. (1996).	Reconstruction and replication study of the Harvard Six Cities time-series study. The original investigators provided PM data; Klemm et al. reconstructed daily mortality and weather data from public records. Data analytical design (GAM Poisson model) was the same as that from the original study.	The combined PM effect estimates were essentially equivalent to the original results.	Total mortality percent excess risks: $PM_{10/15}$: 4.1(2.8, 5.4) per 50µg/m^3 $PM_{2.5}$: 3.3(2.3, 4.3) per 25 µg/m^3 $PM_{10-2.5}$: 1.0(-0.4, 2.4) per 25 µg/m^3
Klemm and Mason (2003). Re-analysis of the above study.	Re-analysis of the above study using GAM with stringent convergence criteria and GLM/natural splines. Sensitivity of results to alternative degrees of freedom were also examined.	When GAM with stringent convergence criteria were applied, PM effect estimates were reduced by 10 to 15%. GLM/natural splines, and increasing the degrees of freedom for temporal trends resulted in further reductions in PM coefficients.	Total mortality percent excess risks using GAM stringent convergence criteria: $PM_{10/15}$: 3.5(2.0, 5.1) per 50µg/m^3 $PM_{2.5}$: 3.0(2.1, 4.0) per 25 µg/m^3 $PM_{10-2.5}$: 0.8(-0.5, 2.0) per 25 µg/m^3 Using GLM/natural splines: $PM_{10/15}$: 2.0(0.3, 3.8) per 50µg/m^3 $PM_{2.5}$: 2.0(0.9, 3.2) per 25 µg/m^3 $PM_{10-2.5}$: 0.3(-1.2, 1.8) per 25 µg/m
Schwartz (2003a). Re-analysis of the Harvard Six Cities time-series analysis.	$PM_{2.5}$ data were re-analyzed using GAM with stringent convergence criteria, GLM/natural splines, B-splines, penalized splines, and thin-plate splines.	When GAM with stringent convergence criteria were applied, $PM_{2.5}$ effect estimates were reduced by ~5%. GLM/natural splines, B-splines, penalized splines, and thin-plate splines each resulted in further reductions in $PM_{2.5}$ excess risk estimates.	Total mortality percent excess risks using per 25 µg/m^3 $PM_{2.5}$: GAM (default):3.7(2.7, 4.7) GAM (stringent): 3.5(2.5, 4.5) Natural splines: 3.3(2.2, 4.3) B-splines: 3.0(2.0, 4.0) Penalized splines: 2.9(1.8, 4.) Thin-plate splines: 2.6(1.5, 3.8)
Zeger et al. (1999). Philadelphia, 1974-1988.	The implication of harvesting for PM regression coefficients, as observed in frequency domain, was illustrated using simulation. Three levels of harvesting, 3 days, 30 days, and 300 days were simulated. Real data from Philadelphia was then analyzed.	In the simulation results, as expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the Philadelphia data, the regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range.	
Dominici et al. (2003). Re-analysis of above study.	Re-analysis of above model using GLM/natural splines.	Results were essentially unchanged.	

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

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 50 $\mu g/m^3$ PM_{10} were 14.2%(7.8, 21.1) , 8.8%(0.6, 17.7), 5.1%(3.0, 7.2), and 3.0%(0.0, 6.2) for pneumonia, COPD, all cardiovascular, and myocardial infarction mortality, respectively.
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as penalized splines.	Small changes in PM risk estimates. Original findings unchanged.	Above estimates using stringent convergence criteria were: 16.5%(8.3, 25.3), 9.9%(0.6, 20.0), 5.1%(2.8, 7.5), and 3.5%(-0.7, 8.0). Corresponding numbers for penalized splines were: 11.5%(3.1, 20.6), 7.2%(-2.6, 18.0), 4.6%(2.0, 7.2), and 2.5%(-2.2, 7.5).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000a).* Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	Daily total (non-accidental) deaths (20, 19, 63, 60, 10, 133, 32, 6, 9, and 29, respectively in these cities in the order shown left). Deaths stratified by location of death (in or outside hospital) were also examined. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. The data were also analyzed by season (November through April as heating season). In the second stage, the PM_{10} coefficients were modeled as a function of city-dependent covariates including copollutant to PM_{10} regression coefficient (to test confounding), unemployment rate, education, poverty level, and percent non-white. Threshold effects were also examined. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	PM_{10} was significantly associated with total deaths, and the effect size estimates were the same in summer and winter. Adjusting for other pollutants did not substantially change PM_{10} effect size estimates. Also, socioeconomic variables did not modify the estimates. The effect size estimate for the deaths that occurred outside hospitals was substantially greater than that for inside hospitals. The effect size estimate was larger for subset with PM_{10} less than 50 g/m^3.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.4 (2.7, 4.1); summer 3.4 (2.4, 4.4); winter 3.3 (2.3, 4.4); in-hospital 2.5 (1.5, 3.4); out-of-hospital 4.5 (3.4, 5.6); days < 50 $\mu g/m^3$ 4.4 (3.1, 5.7); with SO_2 2.9 (1.2, 4.6); with CO 4.6 (3.2, 6.0); with O_3 3.5 (1.6, 5.3).
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. The case for in vs. out of hospital deaths and days $PM_{10} < 50$ $\mu g/m^3$ were not re-analyzed.		The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.3 (2.6, 4.1); summer 3.4 (2.5, 4.4); winter 3.1 (2.0, 4.1); with SO_2 3.2 (1.7, 4.8); with CO 4.5 (2.7, 6.4); with O_3 3.5 (2.2, 4.8). Corresponding values for natural splines are: overall 2.8 (2.0, 3.6); summer 2.6 (1.6, 3.7); winter 2.9 (1.8, 4.1); with SO_2 2.8 (1.0, 4.6); with CO 3.7 (1.6, 5.8); with O_3 3.0 (1.6, 4.4).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000b).* Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	The issue of distributed lag effects was the focus of this study. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were examined using four models: (1) 1-day mean at lag 0 day; (2) 2-day mean at lag 0 and 1 day; (3) second-degree distributed lag model using lags 0 through 5 days; (4) unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	The effect size estimates for the quadratic distributed model and unconstrained distributed lag model were similar. Both distributed lag models resulted in substantially larger effect size estimates than the single day lag, and moderately larger effect size estimates than the two-day average models.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 3.3 (2.5, 4.1) for 1-day mean at lag 0; 5.4 (4.4, 6.3) 2-day mean of lag 0 and 1; 7.3 (5.9, 8.6) for quadratic distributed lag; and 6.6 (5.3, 8.0) for unconstrained distributed lag.
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as penalized splines. Only quadratic distributed lag and unconstrained distributed lag models were re-analyzed.	PM risk estimates were reduced but not substantially. Original findings unchanged.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 6.3 (4.9, 7.8) for quadratic distributed lag; and 5.8 (4.4, 7.3) for unconstrained distributed lag using stringent convergence criteria. Corresponding numbers for penalized splines were: 5.3%(4.2, 6.5) and 5.3%(3.9).
Schwartz and Zanobetti (2000). + Ten U.S. cities. Same as above.	The issue of a threshold in PM-mortality exposure-response curve was the focus of this study. First, a simulation was conducted to show that the "meta-smoothing" could produce unbiased exposure-response curves. Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were used to generate mortality series in 10 cities, and GAM Poisson models were used to estimate exposure response curve. Effects of measurement errors were also simulated. In the analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature, dewpoint, and barometric pressure, and day-of-week. Smooth function of PM_{10} with the same span (0.7) in each of the cities. The predicted values of the log relative risks were computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the predicted values were combined across cities using inverse-variance weighting.	The simulation results indicated that the "meta-smoothing" approach did not bias the underlying relationships for the linear and threshold models, but did result in a slight downward bias for the logarithmic model. Measurement error (additive or multiplicative) in the simulations did not cause upward bias in the relationship below threshold. The threshold detection in the simulation was not very sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.	The combined exposure-response curve indicates that an increase of 50 $\mu g/m^3$ is associated with about a 4% increase in daily deaths. Avg. of 0 and 1 day lags.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
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 μg/m^3 increase of mean of lag 0- and 1-days PM_{10}: white 5.0 (4.0, 6.0); black 3.9 (2.3, 5.4); male 3.8 (2.7, 4.9); female 5.5 (4.3, 6.7); education <12y 4.7 (3.3, 6.0); education > 12y 3.6 (1.0, 6.3).
Moolgavkar (2000a)* Cook County, Illinois Los Angeles County, CA Maricopa County, AZ 1987-1995 PM_{10}, CO, O_3, NO_2, SO_2 in all three locations. $PM_{2.5}$ in Los Angeles County. Cook Co: PM_{10} Median = 47 μg/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 μg/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 μg/m^3 $PM_{2.5}$ 0.5% lags 0, 1 for Los Angeles. Maximum estimated COPD % excess deaths (95% CI) per 50 μg/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/m^3 $PM_{2.5}$ in LA 2.7 (-3.4, 9.1). CVD % per 50 μg/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 μg/m^3 $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1; with CO 0.60 (-2.1, 3.4). CrD % per 50 μg/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 μg/m^3 $PM_{2.5}$, LA 3.6 (-0.6, 7.9) lag 3.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar (2003). Re-analysis of above study, but Maricopa Co. data were not analyzed.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Cerebrovascular deaths data were not analyzed. Ozone was not analyzed. In addition to the 30 degrees of freedom used for smoothing splines for temporal trends in the original analysis, results for 100 degrees of freedom were also presented. Two-pollutant model results were not reported for Cook county.	The sensitivity of results to the degrees of freedom was often greater than that to the GAM convergence criteria. The main conclusion of the original study remained the same.	Maximum estimated non-accidental deaths % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 2.4 (1.3,3.5), lag 0; LA 2.4 (0.5, 4.4) lag2; with CO, -1.6(-3.7, 0.6); per 25 $\mu g/m^3$ $PM_{2.5}$ in LA 1.5 (0, 3.0). Maximum estimated COPD % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 5.5 (0.3,11.0), lag 2; LA 4.4 (-3.1, 12.6) lag 1; per 25 $\mu g/m^3$ $PM_{2.5}$ in LA 1.9 (-10.0, 15.4). CVD % per 50 $\mu g/m^3$ PM_{10}: Cook 2.2 (0.3, 4.1) lag 3; LA 4.5 (1.6, 7.5) lag 2; Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1. All the estimates above are for 30 degrees of freedom cases.
Ostro et al. (1999a).+ Coachella Valley, CA. 1989-1992. PM_{10} (beta-attenuation) Mean = 56.8 $\mu g/m^3$.	Study evaluated total, respiratory, cardiovascular, non-cardiorespiratory and age >50 yr deaths (mean = 5.4, 0.6, 1.8, 3.0, and 4.8 per day, respectively). The valley is a desert area where 50-60% of PM_{10} estimated to be coarse particles. Correlation between gravimetric and beta-attenuation, separated by 25 miles, was high (r = 0.93). Beta-attenuation data were used for analysis. GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used. Seasonally stratified analyses were also conducted. Lags 0-3 days (separately) of PM_{10} along with moving averages of 3 and 5 days examined, as were O_3, NO_2, and CO.	Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined, except non-cardiorespiratory series. The effect size estimates for total and cardiovascular deaths were larger for warm season (May through October) than for all year period. NO_2 and CO were significant predictor of mortality in single pollutant models, but in multi-pollutant models, none of the gaseous pollutants were significant (coefficients reduced), whereas PM_{10} coefficients remained the same and significant.	Total mortality percent excess deaths per 50 $\mu g/m^3$ PM_{10} at 2-day lag = 4.6 (0.6, 8.8). Cardiac deaths: 8.33 (2.14, 14.9) Respiratory deaths: 13.9 (3.25, 25.6)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ostro et al. (2000).* Coachella Valley, CA. 1989-1998. $PM_{2.5}$ = 16.8; $PM_{10-2.5}$ = 25.8 in Indio; $PM_{2.5}$ = 12.7; $PM_{10-2.5}$ = 17.9 in Palm Springs.	A follow-up study of the Coachella Valley data, with $PM_{2.5}$ and $PM_{10-2.5}$ data in the last 2.5 years. Both $PM_{2.5}$ and $PM_{10-2.5}$ were estimated for the remaining years to increase power of analyses. However, only $PM_{10-2.5}$ could be reliably estimated. Therefore, predicted $PM_{2.5}$ data were not used for mortality analysis. Thus, the incomparable sample size make it difficult to directly assess the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ in this data set.	Several pollutants were associated with all-cause mortality, including $PM_{2.5}$, CO, and NO_2. More consistent results were found for cardiovascular mortality, for which significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not $PM_{2.5}$ (possibly due to low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data).	Total percent excess deaths: PM_{10} (lag 0 or 2) = 2.0 (-1.0, 5.1) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 11.5 (0.2, 24.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0 or 2) = 1.3 (-0.6, 3.5) per 25 $\mu g/m^3$ Cardio deaths: PM_{10} (lag 0) = 6.1 (2.0, 10.3) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 8.6 (-6.4, 25.8) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0) = 2.6 (0.7, 4.5) per 25 $\mu g/m^3$ Respiratory deaths: PM_{10} (lag 3) = -2.0 (-11.4, 8.4) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 1) = 13.3 (-43.1, 32.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 3) = -1.3 (-6.2, 4.0) per 25 $\mu g/m^3$
Ostro et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Only cardiovascular mortality data were analyzed. Additional sensitivity analyses were conducted.	The PM risk estimates were slightly reduced with stringent convergence criteria and GLM. Sensitivity analysis showed that results were not sensitive to alternative degrees of freedom for temporal trends and temperature. Multi-day averages for PM increased risk estimates.	Cardio deaths (GAM with stringent convergence criteria): PM_{10} (lag 0) = 5.5 (1.6, 9.5) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 10.2 (-5.3, 28.3) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0) = 2.9 (0.7, 5.2) per 25 $\mu g/m^3$ Cardio deaths (GLM/natural splines): PM_{10} (lag 0) = 5.1 (1.2, 9.1) per 50 $\mu g/m^3$ $PM_{2.5}$ (only 0-2 day lags reported) $PM_{10-2.5}$ (lag 0) = 2.7 (0.5, 5.1) per 25 $\mu g/m^3$

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

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); $PM_{10\text{-}2.5}$ (11); COH (0.5 unit); NO_3 (3.0); SO_4 (1.8)	Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, 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 $PM_{10\text{-}2.5}$) were significantly associated in single poll. models. In 2 and 4 poll. models with $PM_{2.5}$ or nitrate, other pollutants were not significant. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that COH was very significantly associated with mortality.	Total mortality per 25 $\mu g/m^3$ $PM_{2.5}$ at 0 d lag: 8% in one pollutant model; 9-12% in 2 pollutant model except with NO_3(~0) . Also, 8% per 50 $\mu g/m^3$ PM_{10} in one pollutant model and 2% per 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$. Cardiovascular mortality: PM_{10} = 9% per 50 $\mu g/m^3$ $PM_{2.5}$ = 13% per 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$ = 3% per 25 $\mu g/m^3$ Respiratory mortality: PM_{10} = 11% per 50 $\mu g/m^3$ $PM_{2.5}$ = 7% per 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$ = 16% per 25 $\mu g/m^3$
Fairley (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines.	PM coefficients were either unchanged, slightly decreased, or slightly increased. Original findings, including the pattern in two-pollutant models unchanged.	Percent excess mortality for GAM (stringent) and GLM/natural splines, respectively per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Total mortality: PM_{10} =7.8(2.8,13.1); 8.3(2.9, 13.9) $PM_{2.5}$ = 8.2(1.6, 15.2); 7.1(1.4, 13.1) $PM_{10\text{-}2.5}$ = 4.5(-7.6, 18.1); 3.3(-5.3, 12.7) Cardiovascular mortality: PM_{10} = 8.5(0.6, 17.0); 8.9(1.3, 17.0) $PM_{2.5}$ = 6.4(-4.1, 18.1); 6.8(-2.5, 16.9) $PM_{10\text{-}2.5}$ = 5.1(-13.4, 27.4); (no GLM) Respiratory mortality: PM_{10} = 10.7(-3.7, 27.2); 10.8(-3.4, 27.1) $PM_{2.5}$ = 11.8(-9.9, 38.7); 13.6(-3.7, 34.1) $PM_{10\text{-}2.5}$ = 32.2(-12.1, 98.6); (no GLM)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz et al. (1999). Spokane, WA 1989-1995 PM_{10}: "control" days: 42 µg/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 µg/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 µg/m^3; all PM_{10} % per 50 µg/m^3.
Schwartz and Zanobetti (2000) +Chicago 1988-1993. PM_{10}. Median = 36 µg/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 µg/m^3 increase of mean of lag 0- and 1-days PM_{10}: total deaths 4.5 (3.1, 6.0); in-hospital 3.9 (2.1, 5.8); out-of-hospital 6.3 (4.1, 8.6). For total deaths, the RR approximately doubles as the time scale changes from 15 days to 60 days. For out-of-hospital deaths, it triples from15 days to 60 days time scale.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Lippmann et al. (2000).* Detroit, MI. 1992-1994. PM_{10} = 31; $PM_{2.5}$ = 18; $PM_{10-2.5}$ = 13.	For 1992-1994 study period, total (non-accidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO.	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ effect size estimates were comparable per same distributional increment (5^{th} to 95^{th} percentile).	Percent excess mortality per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$: Total mortality: PM_{10} (1 d) = 4.4(-1.0,10.1) $PM_{2.5}$ (3 d) = 23.1(-0.6, 7.0) $PM_{10-2.5}$ (1 d) = 4.0(-1.2, 9.4)
For 1985-1990 period TSP, PM_{10}, TSP-PM_{10}, Sulfate from TSP (TSP-$SO_4^=$)	For earlier 1985-1990 study period, total non-accidental, circulatory, respiratory, and "other" (non-circulatory or respiratory non-accidental) mortality were evaluated versus noted PM indices and gaseous pollutants.	Both PM_{10} (lag 1 and 2 day) and TSP (lag 1 day) but not TSP-PM_{10} or TSP-$SO_4^=$ significantly associated with respiratory mortality for 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM_{10} or TSP reduced PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.	Circulatory mortality: PM_{10} (1 d) = 6.9(-1.3, 15.7) $PM_{2.5}$ (1 d) = 3.2 (-2.3, 8.9) $PM_{10-2.5}$ (1 d) = 7.8 (0, 16.2) Respiratory mortality: PM_{10} (0 d) = 7.8(-10.2, 29.5) $PM_{2.5}$ (0 d) = 2.3 (-10.3, 16.6) $PM_{10-2.5}$ (2 d) = 7.4(-9.1, 26.9)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ito (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Additional sensitivity analysis examined alternative weather models and influence of the degrees of freedom in a limited data sets.	PM coefficients were often reduced (but sometimes unchanged or increased) somewhat when GAM with stringent convergence criteria or GLM/natural splines were used. The reductions in coefficients were not differential across PM components; the original conclusion regarding the relative importance of PM components remained the same.	Percent excess mortality for GAM (stringent) and GLM/natural splines, respectively per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$: Total mortality: PM_{10} (1 d) = 3.3(-2.0, 8.9); 3.1(-2.2, 8.7) $PM_{2.5}$ (3 d) = 1.9 (-1.8,5.7); 2.0(-1.7, 5.8) $PM_{10-2.5}$ (1 d) = 3.2(-1.9, 8.6); 2.8(-2.2, 8.1) Circulatory mortality: PM_{10} (1 d) = 5.4(-2.6, 14.0); 4.9(-3.0, 13.5) $PM_{2.5}$ (1 d) = 2.2 (-3.2, 7.9); 2.0(-3.4, 7.7) $PM_{10-2.5}$ (1 d) = 6.7 (-1.0, 15.0); 6.0(-1.6, 14.3) Respiratory mortality: PM_{10} (0 d) = 7.5(-10.5, 29.2); 7.9(-10.2, 29.7) $PM_{2.5}$ (0 d) = 2.3 (-10.4, 16.7); 3.1(-9.7, 17.7) $PM_{10-2.5}$ (2 d) = 7.0(-9.5, 26.5); 6.4(-10.0, 25.7)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Chock et al. (2000). 1989-1991 Pittsburgh, PA PM_{10} (daily) $PM_{2.5}$ (every 2 days)	Study evaluated associations between daily mortality and several air pollution variables (PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2) in two age groups (<75 yr., 75 yr.) in Pittsburgh, PA, during 3-yr. period. Poisson GLM regression used, including filtering of data based on cubic B-spline basis functionsas adjustments for seasonal trends. Day-of-week effects, temperature was modeled as a V-shape terms. Single- and multi-pollutant models run for 0, 1, 2, and 3 day lags. $PM_{2.5}/PM_{10}$ 0.67.	Issues of seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients emphasized. Single- and multi-pollutant non-seasonal models show significant positive association between PM_{10} and daily mortality, but seasonal models showed much multi-collinearity, masking association of any pollutant with mortality. Also, based on data set half the size for PM_{10}, the $PM_{2.5}$ coefficients were highly unstable and, since no consistently significant associations found in this small data set stratified by age group and season, no conclusions drawn on relative role of $PM_{2.5}$ vs. $PM_{10-2.5}$.	Total mortality percent increase per 25 µg/m^3 for aged <75 yrs: $PM_{2.5}$ = 2.6% (2.0, 7.3) $PM1_{0-2.5}$ = 0.7% (-1.7, 3.7) Total mortality percent increase per 25 µg/m^3 for aged >75 yrs: $PM_{2.5}$ = 1.5% (-3.0, 6.3) $PM1_{0-2.5}$ = 1.3% (-1.3, 3.8)
Klemm and Mason (2000). Atlanta, GA 1998-1999 $PM_{2.5}$ mean=19.9; $PM_{2.5}/PM_{10}$ =0.65. Nitrate, EC, OC, and oxygenated HC.	Reported "interim" results for 1 yr period of observations regarding total mortality in Atlanta, GA during 1998-1999. Poisson GLM model with natural splines used to assess effects of $PM_{2.5}$ vs $PM_{10-2.5}$, and for nitrate, EC, OC and oxygenated HC components.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.	Total mortality percent increase per 25 µg/m^3 for: $PM_{2.5}$ = 4.8% (-3.2, 13.4) $PM_{10-2.5}$ = 1.4% (-11.3, 15.9)
Gwynn et al. (2000). +Buffalo, N.Y. 1988-1990. PM_{10} (24); COH (0.2 /1000ft); SO_4 = (62 nmoles/m3)	Total, circulatory, and respiratory mortality and unscheduled hospital admissions were analyzed for their associations with H+, SO_4=, PM_{10}, COH, O_3, CO, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, humidity, using. Poisson and negative binomial GAM models.	For total mortality, all the PM components were significantly associated, with H+ being the most significant, and COH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality.	12% (2.6, 22.7) per 50 µg/m^3 PM_{10} at 2-day lag.
Schwartz (2000c).* Boston, MA. 1979-1986. $PM_{2.5}$ mean = 15.6.	Non-accidental total, pneumonia, COPD, and ischemic heart disease mortality were examined for possible "harvesting" effects of PM. The mortality, air pollution, and weather time-series were separated into seasonal cycles (longer than 2-month period), midscale, and short-term fluctuations using STL algorithm. Four different midscale components were used (15, 30, 45, and 60 days) to examine the extent of harvesting. GAM Poisson regression analysis was performed using deaths, pollution, and weather for each of the four midscale periods.	For COPD deaths, the results suggest that most of the mortality was displaced by only a few months. For pneumonia, ischemic heart disease, and total mortality, the effect size increased with longer time scales.	Total mortality percent increase per 25 µg/m^3 increase in $PM_{2.5}$: 5.8(4.5, 7.2) for 15-day window fluctuations; 9.6 (8.2, 11.1) for the 60 day window.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2003a). Re-analysis of above study.	Reanalysis of above study using GLM/natural splines.	PM risk estimates at different time scales changed only slightly (more often increased). Increase in standard error of PM coefficients was also small (<3%). Original findings unchanged.	Total mortality percent increase per 25 $\mu g/m^3$ increase in $PM_{2.5}$: 5.8 (4.5, 7.3) for 15-day window; 9.7 (8.2, 11.2) for the 60 day window.
Lipfert et al. (2000a). Philadelphia (7 county Metropolitan area), 1992-1995. Harvard PM measurements: $PM_{2.5}$ (17.3); PM_{10} (24.1); $PM_{10-2.5}$ (6.8), sulfate (53.1 nmol/m3); H^+ (8.0 nmol/m3).	12 mortality variables, as categorized by area, age, and cause, were regressed on 29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by sub-areas), yielding 348 regression results. Both dependent and explanatory variables were pre-filtered using the19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for hot and cold days and day-of-week using stepwise procedure. The average of current and previous days' pollution levels were used.	Significant associations were found for a wide variety gaseous and particulate pollutants, especially for peak O_3. No systematic differences were seen according particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.	The fractional Philadelphia mortality risk attributed to the pollutant levels: "average risk" was 0.0423 for 25 $\mu g/m^3$ $PM_{2.5}$; 0.0517 for 25 $\mu g/m^3$ $PM_{10-2.5}$; 0.0609 for 50 $\mu g/m^3$ PM_{10}, using the Harvard PM indices at avg. of 0 and 1 d lags.
Laden et. al. (2000)* Six Cities (means): Watertown, MA (16.5); Kingston-Harriman, TN (21.1); St. Louis, MO (19.2); Steubenville, OH (30.5); Portage, WI (11.3); Topeka, KS (12.2). 1979-1988?. 15 trace elements in the dichot $PM_{2.5}$: Si, S, Cl, K, Ca, V, Mn, Al, Ni, Zn, Se, Br, Pb, Cu, and Fe.	Total (non-accidental), ischemic heart disease, pneumonia, and COPD (mean daily total deaths for the six cities: 59, 12, 55, 3, 11, and 3, respectively in the order shown left). A factor analysis was conducted on the 15 elements in the fine fraction of dichot samplers to obtain five common factors; factors were rotated to maximize the projection of the single "tracer" element (as in part identified from the past studies conducted on these data) for each factor; $PM_{2.5}$ was regressed on the identified factors scores so that the factor scores could be expressed in the mass scale. Using GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time, mortality was regressed on the factor scores in the mass scale. The mean of the same-day and previous day (increasing the sample size from 6,211 to 9,108 days) mass values were used. The city-specific regression coefficients were combined using inverse variance weights.	Three sources of fine particles were defined in all six cities with a representative element for each source type: Si for soil and crustal material; Pb for motor vehicle exhaust; and Se for coal combustion sources. In city-specific analysis, additional sources (V for fuel oil combustion, Cl for salt, etc.) were considered. Five source factors were considered for each city, except Topeka with the three sources. Coal and mobile sources account for the majority of fine particles in each city. In all of the metropolitan areas combined, 46% of the total fine particle mass was attributed to coal combustion and 19% to mobile sources. The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality.	Percent excess total mortality per 25µg/m3 increase in PM2.5 from source types: Crustal: -5.6(-13.6, 3.1) Traffic: 8.9(4.2, 13.8) Coal: 2.8(0.8, 4.8) Residual oil: 6.3(0.4, 12.5)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2003a). Re-analysis of above study.	Re-analysis of above study using penalized splines.	The change in risk estimates for each source-apportioned $PM_{2.5}$ in each city were either positive or negative, but the combined estimates across cities increased for traffic factor and decreased for coal factor and residual oil factor.	Percent excess total mortality per 25µg/m3 increase in PM2.5 from source types: Crustal: -5.1(-13.9, 4.6) Traffic: 9.3(4.0, 14.9) Coal: 2.0(-0.3, 4.4) Residual oil: 5.9(-0.9, 13.2)
Levy (1998). King County, WA. 1990-1994. PM_{10} Nephelometer (30); (0.59 bsp unit)	Out-of-hospital deaths (total, respiratory, COPD, ischemic heart disease, heart failure, sudden cardiac death screening codes, and stroke) were related to PM_{10}, nephelometer (0.2 - 1.0 m fine particles), SO_2, and CO, adjusting for day-of-week, month of the year, temperature and dewpoint, using Poisson GLM regression.	Nephelometer data were not associated with mortality. Cause-specific death analyses suggest PM associations with ischemic heart disease deaths. Associations of mortality with SO_2 and CO not mentioned. Mean daily death counts were small (e.g., 7.7 for total; 1.6 for ischemic heart disease). This is an apparently preliminary analysis.	Total mortality percent excess: 5.6% (-2.4, 14.3) per 50 µg/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 µg/m^3 PM_1; -1.0 (-8.7,. 7.7) with SO_2 and CO.
Mar et al. (2000).* Phoenix, AZ. 1995-1997. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (TEOM), with means = 46.5, 13.0, and 33.5, respectively; and $PM_{2.5}$ (DFPSS), mean = 12.0.	Total (non-accidental) and cardiovascular deaths (mean = 8.6 and 3.9, respectively) for only those who resided in the zip codes located near the air pollution monitor were included. GAM Poisson models were used, adjusting for season, temperature, and relative humidity. Air pollution variables evaluated included: O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days evaluated. Factor analysis also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores included in mortality regression.	Total mortality was significantly associated with CO and NO_2 and weakly associated with SO_2, PM_{10}, $PM_{10-2.5}$, and EC. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, OC and EC. Combustion-related factors and secondary aerosol factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality.	Total mortality percent excess: 5.4 (0.1, 11.1) for PM_{10} (TEOM) 50 µg/m^3 at lag 0 d; 3.0 (-0.5, 6.6) for $PM_{10-2.5}$ (TEOM) 25 µg/m^3 at lag 0 d; 3.0 (-0.7, 6.9) for $PM_{2.5}$ (TEOM) 25 µg/m^3 at lag 0 d. Cardiovascular mortality RRs: 9.9 (1.9, 18.4) for PM_{10} (TEOM) 50 µg/m^3 at lag 0 d; 18.7 (5.7, 33.2) for $PM_{2.5}$ (TEOM) 25 µg/m^3 at lag 1 d; and 6.4 (1.4, 11.7) PM_{10} (TEOM) 25 µg/m^3 $PM_{10-2.5}$ at lag 0 d.
Mar et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Only cardiovascular mortality was re-analyzed.	Reductions on PM risk estimates for PM mass concentration indices in the GAM/stringent convergence criteria or GLM/natural splines were small. The change in coefficient for source factors varied: moderate reductions for motor vehicle factor, but slight increase for regional sulfate factor. EC and OC coefficients were also slightly reduced.	Percent excess cardiovascular mortality per 50 µg/m^3 PM_{10}; 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$: GAM with stringent convergence criteria and GLM/natural splines, respectively: PM_{10} (0 d): 9.7(1.7, 18.3); 9.5(0.6, 19.3) $PM_{2.5}$ (1 d): 18.0(4.9, 32.6); 19.1(3.9, 36.4) $PM_{10-2.5}$ (0 d): 6.4(1.3, 11.7); 6.2(0.8, 12.0)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Clyde et al. (2000). Phoenix, AZ. 1995-1998. PM_{10}, and $PM_{2.5}$, (from TEOM), with means = 45.4, and 13.8. $PM_{10-2.5}$ computed as PM_{10}-$PM_{2.5}$.	Elderly (age 65 years) non-accidental mortality for three regions of increasing size in Phoenix urban area analyzed to evaluate influence of spatial uniformity of PM_{10} and $PM_{2.5}$. All-age accidental deaths for the metropolitan area also examined as a "control". GAM Poisson models adjusting for season (smoothing splines of days), and parametric terms for temperature, specific humidity, and lags 0- to 3-d of weather variables. PM indices for lags 0-3 d considered. Bayesian Model Averaging (BMA) produces posterior mean relative risks by weighting each model (out of all possible model specifications examined) based on support received from the data.	The BMA results suggest that a weak association was found only for the mortality variable defined over the region with uniform $PM_{2.5}$, with a 0.91 probability that RR is greater than 1. The other elderly mortality variables, including the accidental deaths ("control"), had such probabilities in the range between 0.46 to 0.77. Within the results for the mortality defined over the region with uniform $PM_{2.5}$, the results suggested that effect was primarily due to coarse particles rather than fine; only the lag 1 coarse PM was consistently included in the highly ranked models.	Posterior mean RRs and 90% probability intervals per changes of 25 $\mu g/m^3$ in all lags of fine and coarse PM for elderly mortality for uniform PM_{10} region: 1.06 (1+, 1.11).
Smith et al. (2000). Phoenix, AZ. 1995-1997	Study evaluated effects of daily and 2- to 5-day average coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$) particles from an EPA-operated central monitoring site on nonaccidental mortality among elderly (65+ years), using time-series analyses for residents within city of Phoenix and, separately, for region of circa 50 mi around Phoenix. Mortality was square-root transformed.Initial model selected to represent long-term trends (using B-splines) and weather variables (e.g., ave. daily temp., max daily temp., daily mean specific humidity, etc.); then PM variables added to model one at a time to ascertain which had strongest effect. Piecewise linear analysis and spline analysis used to evaluate possible nonlinear PM-mortality relationship and to evaluate threshold possibilities. Data analyzed most likely same as Clyde's or Mar's Phoenix data.	In linear PM effect model, a statistically significant mortality association found with $PM_{10-2.5}$, but not with $PM_{2.5}$. In the model allowing for a threshold, evidence suggestive of possible threshold for $PM_{2.5}$ (in the range of 20-25 $\mu g/m^3$) found, but not for $PM_{10-2.5}$. A seasonal interaction in the $PM_{10-2.5}$ effect was also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10-2.5}$ is lowest.	—

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
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 µg/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 µg/m^3 increase in current day PM_{15}: in Newark, 5.7 (4.6, 6.7) for total mortality, 7.8 (3.6, 12.1) for cardioresp. mortality; in Camden, 11.1 (0.7, 22.5) and 15.0 (4.3, 26.9); and in Elizabeth, -4.9 (-17.9, 10.9) and 3.0 (-11.0, 19.4), respectively. Percent excess deaths per 25 µg/m^3 $PM_{2.5}$; in Newark, 4.3 (2.8, 5.9) for total and 5.1 (3.1, 7.2) for cardiorespiratory mortality; in Camden, 5.7 (0.1, 11.5) and 6.2 (0.6, 12.1); in Elizabeth, 1.8 (-5.4, 9.5) and 2.3 (-5.0, 10.1), respectively.
Gamble (1998). Dallas, TX. 1990-1994. PM_{10} (25)	Relationships of total, respiratory, cardiovascular, cancer, and remaining non-accidental deaths to PM_{10}, O_3, NO_2, SO_2, and CO evaluated, adjusting for temperature, dewpoint, day-of-week, and seasonal cycles (trigonometric terms) using Poisson GLM regression.	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 µg/m^3 PM_{10} at 0 lag (other lags also reported to have no associations)
Ostro (1995). San Bernardino and Riverside Counties, CA, 1980-1986. $PM_{2.5}$ (estimated from visual range). Mean = 32.5.	Study evaluated total, respiratory, cardiovascular, and age > = 65 deaths (mean = 40.7, 3.8, 18.7, and 36.4 per day, respectively). $PM_{2.5}$ estimated based on airport visual range and previously published empirical formula. Autoregressive OLS (for total) and Poisson (for sub-categories) regressions used, adjusting for season (sine/cosine with cycles from 1 yr to 0.75 mo; prefiltering with 15-day moving ave.; dichotomous variables for each year and month; smooth function of day and temp.), day-of-week, temp. and dewpoint. Evaluated lags 0, 1, and 2 of estimated $PM_{2.5}$, as well as moving averages of 2, 3, and 4 days and O_3.	The results were dependent on season. No $PM_{2.5}$ – mortality association found for the full year-round period. Associations between estimated $PM_{2.5}$ (same-day) and total and respiratory deaths found during summer quarters (April - Sept.). Correlation between the estimated $PM_{2.5}$ and daily max temp. was low (r = 0.08) during the summer quarters. Ozone was also associated with mortality, but was also relatively highly correlated with temp. r = 0.73). Moving averages of $PM_{2.5}$ did not improve the associations.	Percent excess deaths per 25 µg/m3 of estimated $PM_{2.5}$, lag 0: Full year: 0.3 (-0.6, 1.2) for total; 2.1 (-0.3, 4.5) for respiratory; and 0.7 (-0.3, 1.7) for circulatory. Summer quarters: 1.6 (0.03, 3.2) for total; 5.5 (1.1, 10.0) for respiratory; and 0 (-1.0, 1.0) for circulatory.
Kelsall et al. (1997). +Philadelphia, PA 1974-1988. TSP (67)	Total, cardiovascular, respiratory, and by-age mortality regressed on TSP, SO_2, NO_2, O_3, and CO, adjusting for temporal trends and weather, using Poisson GAM model.	TSP, SO_2, O_3, and 1-day lagged CO individually showed statistically significant associations with total mortality. No NO_2 associations unless SO_2 or TSP was also considered. The effects of TSP and SO_2 were diminished when both pollutants were included.	Total mortality excess risk: 3.2% (0, 6.1) per 100 µg/m^3 TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar and Luebeck (1996). Philadelphia, PA. 1973-1988. TSP (68)	A critical review paper, with an analysis of total daily mortality for its association with TSP, SO_2, NO_2, and O_3, adjusting for temporal trends, temperature, and also conducting analysis by season, using Poisson GAM model. (Only one non-parametric smoothing terms in GAM models)	RR results presented as figures, and seasonal difference noted. TSP, SO_2, O_3 - mortality associations varied across season. TSP associations were stronger in summer and fall. NO_2 was the most significant predictor.	Total mortality excess risk: ranged 0 (winter) to 4% (summer) per 100 µg/m^3 TSP at 1 day lag.
Murray and Nelson (2000). Philadelphia, PA, 1973-1990.	Kalman filtering used to estimate hazard function in a state space model. The model framework, which assumes harvesting effect, allows estimation of at-risk population and the effect of changes in air quality on the life expectancy of the at-risk population. The model was first verified by simulation. Combinations of TSP, linear temperature, squared temperature, and interaction of TSP and temperature were considered in six models.	Both TSP and the product of TSP and average temperature are significant, but not together. The size of at-risk population estimated was about 500 people, with its life expectancy between 11.8 to 14.3 days, suggesting that the hazard causing agent making the difference of 2.5 days in the at-risk population.	The coefficients obtained in the models cannot be directly compared to the relative risk per µg/m^3 PM obtained in other time-series models.
Smith et al. (1999). Birmingham, AL 1985-1988; Chicago (Cook Co.), IL, 1986-1990. PM_{10} median = 45 µg/m^3 for Birmingham and 37.5 µg/m^3 for Chicago.	Study evaluated associations between lagged/averaged PM_{10} and non-accidental mortality in two cities. Mortality was square root-transformed in Birmingham data, and log-transformed in Chicago data. Seasonal cycles were modeled using B-splines. Temperature was modeled using piece-wise linear terms with a change point. PM_{10} data were included in the models at lag 0 through 3 and 3-day averages at these lags. Also, to examine the possible existence of a threshold, PM_{10} was modeled using a B-spline representation, and also using parametric threshold model, with the profile log likelihood evaluated at changing threshold points. In addition, the possibility of mortality displacement was examined with a model that attempts to estimate the frail population size through Bayesian techniques using Monte Carlo sampling.	The authors reported that, while significantly positive associations were found in both cities, the results were sensitive to the choice of lags. The PM_{10}-mortality associations were more stable in Chicago (perhaps in part due to sample size). The non-linear estimates of relative risk using B-splines suggest that an increasing effect above 80µg/m^3 for Birmingham, and above 100 µg/m^3 for Chicago. The threshold model through examination of log likelihood at various possible threshold levels also suggested similar change points, but not to the extent that could achieve statistical distinctions. The mortality displacement model in Chicago data suggested that the size of the frail population was very small (mean ~765), and the mean lifetime within the frail population short (< 10 days).	Birmingham: 4.8%(t=1.98) per 50µg/m^3 change in 1 through 3 day lag average of PM_{10}. Chicago: 3.7% (t=3.17) per 50µg/m^3 change in 0 through 2 day lag average of PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Neas et. al. (1999). Philadelphia. 1973-1980. TSP mean = 77.2.	Total, age over 65, cancer, and cardiovascular deaths analyzed for association with TSP. Conditional logistic regression analysis with case-crossover design conducted. Average values of current and previous days' TSP used. Case period is the 48-hr period ending at midnight on day of death. Control periods are 7, 14, and 21 days before and after the case period. Other covariates included temperature on the previous day, dewpoint on the same day, an indicator for hot days (> 80°F), an indicator for humid days (dewpoint > 66°F), and interaction of same-day temp. and winter season.	In each set of the six control periods, TSP was associated with total mortality. A model with four symmetric reference periods 7 and 14 days around the case period produced a similar result. A model with only two symmetric reference periods of 7 days around the case produced a larger estimate. A larger effect was seen for deaths in persons 65 years of age and for deaths due to pneumonia and to cardiovascular disease. Cancer mortality was not associated with TSP.	Odds Ratio (OR) for all cause mortality per 100 µg/m^3 increase in 48-hr mean TSP was 1.056 (1.027, 1.086). The corresponding number for those aged 65 and over was 1.074 (1.037, 1.111), and 1.063 (1.021, 1.107) for cardiovascular disease.
Schwartz (2000d). +Philadelphia. 1974-1988. TSP. Mean = 70 µg/m^3 for warm season (April through August) and 64 µg/m^3 for cold season.	Total (non-accidental) deaths analyzed. GAM Poisson models adjusting for temperature, dewpoint, day-of-week, and season applied to each of 15 warm and cold seasons. Humidity-corrected extinction coefficient, derived from airport visual range, also considered as explanatory variable. In the second stage, resulting 30 coefficients were regressed on regression coefficients of TSP on SO_2. Results of first stage analysis combined using inverse variance weighting.	When TSP controlled for, no significant association between SO_2 and daily deaths. SO_2 had no association with daily mortality when it was poorly correlated with TSP. In contrast, when SO_2 was controlled for, TSP was more strongly associated with mortality than when it was less correlated with SO_2. However, all of the association between TSP and mortality was explained by its correlation with extinction coefficient.	Total mortality excess risk estimates combined across seasons/years: 9.0 (5.7, 12.5) per 100 µg/m^3 TSP.
Levy et al. (2000). Years vary from study to study ranging between 1973 to 1994. 21 published studies included U.S., Canadian, Mexican, European, Australian, and Chilean cities. PM_{10} levels in the 19 U.S. cities (in some cases TSP were converted to PM_{10} using factor of 0.55) ranged from ~20 to ~60 uµg/m^3.	To determine whether across-study heterogeneity of PM effects could be explained by regional parameters, Levy et al. applied an empirical Bayes meta-analysis to 29 PM estimates from 21 published studies. They considered such city-specific variables as mortality rate, gaseous pollutants regression coefficients, PM_{10} levels, central air conditioning prevalence, heating and cooling degreedays. Several of the studies included were those that used GAM with multiple non-parametric smoothing terms.	Among the city-specific variables, $PM_{2.5}/PM_{10}$ ratio was a significant predictor (larger PM estimates for higher $PM_{2.5}/PM_{10}$ ratios) in the 19 U.S. cities data subsets. While the sulfate data were not available for all the 19 cities, the investigators noted that, based on their analysis of the limited data with sulfate for 10 estimates, the sulfate/PM10 ratio was highly correlated with both the mortality (r = 0.84) and with the $PM_{2.5}/PM_{10}$ ratio (r = 0.70). This indicates that the sulfate/PM_{10} ratio may be even better predictor of regional heterogeneity of PM RR estimates.	The pooled estimate from 19 U.S. cities was 0.70% (0.54, 0.84) per 10 µg/m^3 increase in PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada			
Burnett et al. (1998a).+ 11 Canadian cities. 1980-1991. No PM index data available on consistent daily basis.	Total non-accidental deaths were linked to gaseous air pollutants (NO_2, O_3, SO_2, and CO) using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather (selected from spline-smoothed functions of temperature, dewpoint, relative humidity with 0, 1, and 2 day lags using forward stepwise procedure). Pollution variables evaluated at 0, 1, 2, and up to 3-day lag averages thereof. No PM index included in analyses because daily PM measurements not available. City-specific models containing all four gaseous pollutants examined. Overall risks computed by averaging risks across cities.	NO_2 had 4.1% increased risk per mean concentration; O_3 had 1.8%; SO_2 had 1.4%, and CO had 0.9% in multiple pollutant regression models. A 0.4% reduction in excess mortality was attributed to achieving a sulfur content of gasoline of 30 ppm in five Canadian cities. Daily PM data for fine and coarse mass and sulfates available on varying (not daily) schedules allowed ecologic comparison of gaseous pollutant risks by mean fine particle indicators mass concentrations.	Found suggestion of weak negative confounding of NO_2 and SO_2 effects with fine particles and weak positive confounding of particle effects with O_3. No quantitative RR or ER estimates reported for PM indicators.
Burnett et al. (2000).* 8 largest Canadian cities. 1986-1996. All city mean PM_{10} 25.9; $PM_{2.5}$ 13.3; $PM_{10\text{-}2.5}$ 12.6; sulfate 2.6.	Total non-accidental deaths linked to PM indices (PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, sulfate, 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO). Each city's mortality, pollution, and weather variables separately filtered for seasonal trends and day-of-week patterns. The residual series from all the cities then analyzed in a GAM Poisson model. The weather model was selected from spline-smoothed functions of temperature, relative humidity, and maximum change in barometric pressure within a day, with 0 and 1 day lags using forward stepwise procedure. Pollution effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-pollutant models, principal components were also used as predictors in the regression models.	O_3 was weakly correlated with other pollutants and other pollutants were "moderately" correlated with each other (the highest was r = 0.65 for NO_2 and CO). The strongest association with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger predictor of mortality than $PM_{10\text{-}2.5}$. The estimated gaseous pollutant effects were generally reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10\text{-}2.5}$. Sulfate, Fe, Ni, and Zn were most strongly associated with mortality. Total effect of these four components was greater than that for $PM_{2.5}$ mass alone.	Percentage increase in daily filtered non-accidental deaths associated with increases of 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10\text{-}2.5}$ at lag 1 day: 3.5 (1.0, 6.0) for PM_{10}; 3.0 (1.1, 5.0) for $PM_{2.5}$; and 1.8 (-0.7, 4.4) for $PM_{10\text{-}2.5}$. In the multiple pollutant model with $PM_{2.5}$, $PM_{10\text{-}2.5}$, and the 4 gaseous pollutants, 1.9 (0.6, 3.2) for $PM_{2.5}$; and 1.2 (-1.3, 3.8) for $PM_{10\text{-}2.5}$.
Burnett and Goldberg (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. In the main model of the original analysis, both dependent and independent variables were pre-filtered, but in the re-analysis, co-adjustment (i.e., more common simultaneous regression) approach was used. Additional sensitivity analysis included alternative fitting criteria and changing the extent of smoothing for temporal trends. Only PM_{10}, $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were analyzed. No multiple pollutant models.	In the GAM model (stringent convergence criteria), inclusion of day-of-week variable made moderate increase in PM coefficients (up to 30%). Alternative fitting criteria and degrees of freedom for temporal trends also changed PM coefficients. Generally, larger the degrees of freedom for temporal trends, smaller the PM coefficients. $PM_{10\text{-}2.5}$ were more sensitive to alternative models than $PM_{2.5}$.	Excess total mortality in the GLM/natural splines with knot/2months, and using AIC and White-noise test fitting criteria at 1-day lag: PM_{10}: 2.7(-0.1, 5.5) per 50 $\mu g/m^3$ $PM_{2.5}$: 2.2(0.1, 4.2) per 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$: 1.8(-0.6, 4.4) per 25 $\mu g/m^3$

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Burnett et al. (1998b). + Toronto, 1980-1994. TSP (60); COH (0.42); SO4= (9.2 µg/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 µg/m^3 TSP; 3.5% (1..8, 5.3) per 50 µg/m^3 PM_{10}; 4.8% (3.3, 6.4) per 25 µg/m^3 $PM_{2.5}$. 0 day lag for TSP and PM_{10}; Avg. of 0 and 1 day for $PM_{2.5}$.
Goldberg et al. (2000)* Montreal, Quebec 1984-95 Mean TSP = 53.1 (14.6 - 211.1) µg/m^3 PM_{10} = 32.2 (6.5 - 120.5) µg/m^3 $PM_{2.5}$ = 3.3 (0.0 - 30.0) µg/m^3	Study aimed to shed light on population subgroups that my be susceptible to PM effects. Linked data on daily deaths with other health data from the Quebec Health Insurance Plan (QHIP) (physician visits, pharmaceutical R_x, etc.) to identify individuals with presenting health conditions. PM_{10} and $PM_{2.5}$ measured by dichotomous sampler 1 in 6 days until 1992 (2 stations), then daily through 1993. PM missing days interpolated from COH, ext. coefficient, sulfates. Used quasi likelihood estimation in GAM's to assess PM associations with total and cause-specific mortality; and, also, in subgroups by age and/or preexisting health conditions. Adjusted for CO, NO_2, NO, O_3 and SO_2 in 2-pollutant and all-pollutant models.	Significant associations found for all-cause (total non-accidental) and cause-specific (cancer, CAD, respiratory disease, diabetes) with PM measures. Results reported for $PM_{2.5}$, COH and sulfates. All three PM measures associated with increases in total, resp., and "other nonaccidental", and diabetes-related mortality. No PM associations found with digestive, accidental, renal or neurologic causes of death. Also, mainly in 65+ yr group, found consistent associations with increased total mortality among persons who had cancer, acute lower resp. diseases, any cardiovascular disease, chronic CAD and congestive heart failure (CHF).	Percent excess mortality per 25 µg/m^3 estimated $PM_{2.5}$: Total deaths (3 d ave.) = 4.4% (2.5, 6.3) CV deaths (3 d ave.) = 2.6% (-0.1, 5.5) Resp deaths (3 d ave.) = 16.0% (9.7, 22.8) Coronary artery (3 d ave.) = 3.4% (-0.2, 7.1) Diabetes (3 d ave.) = 15.7% (4.8, 27.9) Lower Resp Disease (3 d ave.) = 9.7% (4.5, 15.1) Airways disease (3 d ave.) = 2.7% (-0.9, 6.4) CHF (3 d ave.) = 8.2% (3.3, 13.4)
Goldberg et al. (2001b)* Montreal, Quebec. 1984-1993. Predicted $PM_{2.5}$ mean = 17.6. CoH (1000ft) mean = 0.24, sulfate mean = 3.3.	The investigators used the universal Quebec medicare system to obtain disease conditions prior to deaths, and the roles of these respiratory and cardiovascular conditions in the PM-mortality associations were examined. GAM Poisson model adjusting for temporal pattern and weather was used.	The PM-mortality associations were found for those who had acute lower respiratory diseases, chronic coronary diseases, and congestive heart failure. They did not find PM-mortality associations for those chronic upper respiratory diseases, airways disease, cerebrovascular diseases, acute coronary artery diseases, and hypertension. Adjusting for gaseous pollutants generally attenuated PM RR estimates, but the general pattern remained. Effects were larger in summer.	The percent excess deaths estimates for non-accidental deaths per IQR (average of 0-2 day lags) for CoH, predicted $PM_{2.5}$, and sulfate were: 1.98% (1.07, 2.90), 2.17% (1.26, 3.08), and 1.29% (0.68, 1.90), respectively.
Goldberg et al. (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.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Goldberg and Burnett (2003). Re-analysis of above studies by Goldberg et al.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Cause-specific mortality was not re-analyzed; re-analysis was focused only on the sub-groups defined using the QHIP data that showed associations with particles in the original study. Sensitivity analyses included alternative weather models and using different degrees of freedom for temporal trends.	The PM coefficients were not very sensitive to the extent of temporal smoothing but were sensitive to the functional form of weather models. Most of the originally reported associations except for congestive heart failure were highly attenuated when natural splines were used for weather model.	The percent excess deaths estimates for non-accidental deaths per IQR (average of 0-2 day lags) for CoH, predicted $PM_{2.5}$, and sulfate for GAM(stringent convergence criteria) and GLM/natural splines, respectively, were: CoH: 1.38, 0.85; Predicted $PM_{2.5}$: 1.57, 0.55; sulfate: 1.03, 0.27. Confidence bands were not given but the GAM results for predicted $PM_{2.5}$ and sulfate were indicated as significant at 0.05 level.
Özkaynak et al. (1996). Toronto, 1970-1991. TSP (80); COH (0.42 /1000ft).	Total, cardiovascular, COPD, pneumonia, respiratory, cancer, and the remaining mortality series were related to TSP, SO_2, COH, NO_2, O_3, and CO, adjusting for seasonal cycles (by high-pass filtering each series) temperature, humidity, day-of-week, using OLS regression. Factor analysis of multiple pollutants was also conducted to extract automobile related pollution, and mortality series were regressed on the resulting automobile factor scores.	TSP (0 day lag) was significantly associated with total and cardiovascular deaths. NO_2 (0-day lag) was a significant predictor for respiratory and COPD deaths. 2-day lagged O_3 was associated with total, respiratory, and pneumonia deaths. Factor analysis showed factor with high loadings for NO_2, COH, and CO (apparently representing automobile factor) as significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.	Total mortality excess risk: 2.8% per 100 µg/m^3 TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe			
Katsouyanni et al. (1997). 12 European (APHEA) cities. 1975-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Athens and Kracow.	Total daily deaths regressed on BS or SO_2 using Poisson GLM models, adjusting for seasonal cycles, day-of-week, influenza epidemic, holidays, temp., humidity. Final analysis done with autoregressive Poisson models to allow for overdispersion and autocorrelation. Pollution effects examined at 0 through 3 day lags and multi-day averages thereof. When city-specific coefficients tested to be homogeneous, overall estimates obtained by computing variance-weighted means of city-specific estimates (fixed effects model). When significant heterogeneity present, source of heterogeneity sought by examining a predefined list of city-specific variables, including annual and seasonal means of pollution and weather variables, number of monitoring sites, correlation between measurements from different sites, age-standardized mortality, proportion of elderly people, smoking prevalence, and geographic difference (north-south, east-west). A random effects model was fit when heterogeneity could not be explained.	Substantial variation in pollution levels (winter mean SO_2 ranged from 30 to 330 µg/m^3), climate, and seasonal patterns were observed across cities. Significant heterogeneity was found for the effects of BS and SO_2, but only the separation between western and central eastern European cities resulted in more homogeneous subgroups. Significant heterogeneity for SO_2 remained in western cities. Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both SO_2 and BS were stronger during the summer and were independent.	Total mortality excess deaths per 25 µg/m^3 increase in single day BS for western European cities: 1.4 (1.0, 1.8); and 2 (1, 3) per 50 µg/m^3 PM_{10} increase. In central/eastern Europe cities, corresponding figure was 0.3 (0.05, 0.5) per 25 µg/m^3 BS.
Samoli et al. (2001). * APHEA 1 cities (see Katsouyanni (1997). At least five years between 1980-1992. The PM levels are the same as those in Katsouyanni et al. (1997).	In order to further investigate the source of the regional heterogeneity of PM effects, and to examine the sensitivity of the RRs, the APHEA data were re-analyzed by the APHEA investigators themselves (Samoli et al., 2001). Unlike previous model in which sinusoidal terms for seasonal control and polynomial terms for weather, the investigators this time used a GAM model with smoothing terms for seasonal trend and weather, which is more commonly used approach in recent years.	T he estimated relative risks for central-eastern cities were larger than those obtained from the previous model. Also, restricting the analysis to days with concentration < 150 µg/m^3 further reduced the differences between the western and central-eastern European cities. The authors concluded that part of the heterogeneity in the estimated air pollution effects between western and central eastern cities in previous publications was caused by the statistical approach and the data range.	Total mortality RRs per 50 µg/m^3 BS for all cities, western cities, and central-eastern cities using the GAM approach were: 2.5% (2.1, 2.9); 3.1% (2.3, 3.8); and, 2.3% (1.7, 2.9), respectively. In contrast, those with old method were: 1.3% (0.9, 1.7); 2.9% (2.1, 3.7); and, 0.6% (0.1, 1.1), respectively.
Samoli et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines.	BS risk estimates using GAM were reduced by ~ 10% when stringent convergence criteria were applied. Use of GLM/natural splines resulted in further and greater reductions.	Results corresponding to above using the GAM with stringent convergence criteria were: 2.3%(1.9, 2.7); 2.7% (2.0, 3.4); and, 2.1% (1.5, 2.7), respectively. Corresponding GLM/natural splines results were: 1.2%(0.7, 1.7); 1.6%(0.8, 2.4); and, 1.0%(0.3, 1.7).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Katsouyanni et al. (2001).* 1990-1997 (variable from city to city). 29 European cities. Median PM_{10} ranged from 14 (Stockholm) to 66 (Prague). Median BS ranged from 10 (Dublin) to 64 (Athens).	The 2nd phase of APHEA (APHEA 2) put emphasis on the effect modification by city-specific factors. The first stage of city specific regressions used GAM Poisson model. The second stage regression analysis was conducted to explain any heterogeneity of air pollution effects using city-specific variables. These city-specific variables included average air pollution levels, average temperature/humidity, age-standardize mortality rate, region indicators, etc.	The authors found several effect modifiers. The cities with higher NO_2 levels showed larger PM effects. The cities with warmer climate showed larger PM effects. The cities with low standardized mortality rate showed larger PM effects.	Total mortality excess risk per 50µg/m3 increase in PM_{10}: Fixed effects model: 3.5(2.9, 4.1) Random effects model: 3.1(2.1, 4.2)
Katsouyanni et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled estimate (random effects estimate) was reduced by 4% when stringent convergence criteria in GAM were used, by 34% when natural splines were used, and by 11% when penalized splines were used. The pattern of effect modification originally reported remained the same. The original findings were unchanged.	Total mortality excess risk per 50µg/m3 increase in PM_{10} using GAM (stringent convergence criteria): 3.3(2.7, 3.9) and 3.0(2.0, 4.1) for fixed effects and random effects models, respectively. Corresponding estimates for GLM/natural splines are: 2.1(1.5, 2.8) and 2.1(1.2, 3.0). Using penalized splines, the estimates are 2.9(2.3, 3.6) and 2.8(1.8, 3.8).
Touloumi et al. (1997). 6 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 14.6 in London to 84.4 in Athens.	Results of the short-term effects of ambient NO_2 and/or O_3 on daily deaths from all causes (excluding accidents) were discussed to provide a basis for comparison with estimated SO_2 or BS effects in APHEA cities. Poisson GLM models, lag/averaging of pollution, and the computation of combined effects across the cities were done in the same way as done by Katsouyanni et al. (1997), as above.	Significant positive associations found between daily deaths and both NO_2 and O_3. Tendency for larger effects of NO_2 in cities with higher levels of BS. When BS included in the model, pooled estimate for O_3 effect only slightly reduced, but coefficient for NO_2 reduced by half. Authors speculated that short-term effects of NO_2 on mortality confounded by other vehicle-derived pollutants.	NO_2 and/or O_3 estimates only.
Zanobetti and Schwartz (2003a). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled PM_{10} (average of 0 and 1 day) mortality risk estimate was reduced by 4% when stringent convergence criteria in GAM were used, by 18% when penalized splines were used. For the 4th degree polynomial distributed lag model, corresponding reductions were 10% and 26%.	Combined total mortality excess risk per 50µg/m^3 increase in the average of 0 and 1 day lag PM_{10} was 3.4(2.0, 4.8) using GAM with stringent convergence criteria. For 4th degree polynomial distributed lag model, it was 7.5(4.4, 10.7). Corresponding reductions using penalized splines were 2.9(1.4, 4.4) and 5.6(1.5, 9.8)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Zmirou et al. (1998). 10 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Kracow.	Cardiovascular, respiratory, and digestive mortality series in10 European cities analyzed to examine cause-specificity of air pollution. The mortality series were analyzed for associations with PM (BS, except TSP in Milan and Bratislava; PM_{13} in Lyon), NO_2, O_3, and SO_2. Poisson GLM models, lag/averaging of pollution, and computation of combined effects across the cities done in the same way as by Katsouyanni et al. (1997), above.	The cardiovascular and respiratory mortality series were associated with BS and SO_2 in western European cities, but not in the five central European cities. NO_2 did not show consistent mortality associations. RRs for respiratory causes were at least equal to, or greater than those for cardiovascular causes. No pollutant exhibited any association with digestive mortality.	Pooled cardiovascular mortality percent excess deaths per 25 µg/m^3 increase in BS for western European cities: 1.0 (0.3, 1.7); for respiratory mortality, it was 2.0 (0.8, 3.2) in single lag day models (the lags apparently varied across cities).
Bremner et al. (1999). London, UK, 1992-1994. BS (13), PM_{10} (29).	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tend to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	1.9% (0.0, 3.8) per 25 µg/m^3 BS at lag 1 day; 1.3% (-1.0, 3.6) per 50 µg/m^3 PM_{10} at lag 1 d for total deaths. Resp. deaths (3 d) = 4.9% (0.5, 9.4). CVD deaths (1 d) = 3.0% (0.3, 5.7).
Prescott et al. (1998). Edinburgh, UK, 1981-1995. PM_{10} (21, by TEOM only for 1992-1995); BS (8.7).	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and >= 65), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson GLM regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	3.8 (1.3, 6.4) per 25 µg/m^3 increase in BS for all cause mortality in age 65+ group, avg. of 1-3 day lags.
Rooney et al. (1998). England and Wales, and Greater London, UK PM_{10} (56, during the worst heat wave; 39, July-August mean)	Excess deaths, by age, sex , and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-94 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987-1992 study (Anderson et al., 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
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 μg/m^3 was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70 μg/m^3 occurred only once during the study period.	5.6% (0.5, 11.0) per 50 μg/m^3 PM_{10} at 1 d lag for total deaths. COPD (1 d lag) deaths = 27.6 (5.1, 54.9). Circulatory (1 d) deaths = 8.8 (1.9, 17.1)
Hoek et al. (2000). * The Netherlands, 1986-1994. PM_{10} (median 34); BS (median 10).	Total, cardiovascular, COPD, and pneumonia mortality series were regressed on PM_{10}, BS, sulfate, nitrate, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model. Deaths occurring inside and outside hospitals were also examined.	Particulate air pollution was not more consistently associated with mortality than were the gaseous pollutants SO_2 and NO_2. Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}. The RRs for all pollutants were larger in the summer months than in the winter months.	Total mortality excess risk estimate per 50 μg/m^3 PM_{10} (average of 0-6 days): 1.2(0.2, 2.2); 0.9(-0.8, 2.7) for CVD; 5.9(0.9, 11.2) for COPD; and 10.1(3.6, 17.1) for pneumonia.
Hoek (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM./natural splines were used.	Total mortality excess risk estimate per 50 μg/m^3 PM_{10} (average of 0-6 days) using GAM with stringent convergence criteria: 1.4(0.3, 2.6); 0.9(-0.8, 2.7) for CVD; 6.1(1.0, 11.4) for COPD; and 10.3(3.7, 17.2) for pneumonia. Corresponding numbers using GLM/natural splines are: 1.2(-0.1, 2.5); 1.6(-0.3, 3.5); 6.0(0.4, 11.8); 10.7 (3.5, 18.3).
Hoek et al. (2001).* The Netherlands. 1986-1994. PM_{10} (median 34); BS (median 10).	This study of the whole population of the Netherlands, with its large sample size (mean daily total deaths ~ 330, allowed examination of specific cardiovascular cause of deaths. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week was used.	Deaths due to heart failure, arrhythmia, cerebrovascular causes, and thrombocytic causes were more strongly (~ 2.5 to 4 times larger relative risks) associated with air pollution than the overall cardiovascular deaths (CVD) or myocardial infarction (MI) and other ischemic heart disease (IHD).	For PM_{10} (7-day mean), RRs for total CVD, MI/IHD, arrhythmia, heart failure, cerebrovascular, and thrombocytic mortality per 50 μg/m^3 increase were:0.9(-0.8, 2.7), 0.3(-2.3, 3.0), 2.5(-4.3, 9.9), 2.2(-2.5, 7.2), 1.9(-1.8, 5.8), and 0.6(-6.8, 8.7) , respectively. The RRs for BS were larger and more significant than those for PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM./natural splines were used.	For PM_{10} (7-day mean), RRs for total CVD, MI/IHD, arrhythmia, heart failure, cerebrovascular, and thrombocytic mortality per 50 µg/m^3 increase using GAM with stringent convergence criteria were:0.9(-0.8, 2.7), 0.4(-2.2, 3.0), 2.7(-4.2, 10.1), 2.4(-2.3, 7.4), 2.0(-1.7, 5.9), and 0.7(-6.8, 8.8) , respectively. The RRs for BS were larger and more significant than those for PM_{10}.
Pönkä et al. (1998). Helsinki, Finland, 1987-1993. TSP (median 64); PM_{10} (median 28)	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson GLM model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant significantly associated with mortality from all cardiovascular or CVD causes in 65+ year age group. Only in age <65 year group, PM_{10} associated with total and CVD deaths with 4 and 5 d lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with CVD mortality <65 yr. group with inconsistent signs and late and spiky lags (neg. on d 5 and pos. on d 6).	18.8% (5.6, 33.2) per 50 µg/m^3 PM_{10} 4 day lag (other lags negative or zero).
Peters et al. (2000b). A highly polluted coal basin area in the Czech Republic and a rural area in Germany, northeast Bavaria districts. 1982-1994. TSP: mean = 121.1 and 51.6, respectively, for these two regions. PM_{10} and $PM_{2.5}$ were also measured in the coal basin during 1993-1994 (mean = 65.9 and 51.0, respectively).	Non-accidental total and cardiovascular deaths (mean = 18.2 and 12.0 per day, for the Czech and Bavaria areas, respectively). The APHEA approach (Poisson GLM model with sine/cosine, temperature as a quadratic function, relative humidity, influenza, day-of-week as covariates), as well as GLM with natural splines for temporal trends and weather terms were considered. Logarithm of TSP, SO_2, NO_2, O_3, and CO (and PM_{10} and $PM_{2.5}$ for 1993-1994) were examined at lags 0 through 3 days.	In the coal basin (i.e., the Czech Republic polluted area), on the average, 68% of the TSP was PM_{10}, and most of PM_{10} was $PM_{2.5}$ (75%). For the coal basin, associations were found between the logarithm of TSP and all-cause mortality at lag 1 or 2 days. SO_2 was also associated with all-cause mortality with slightly lower significance. PM_{10} and $PM_{2.5}$ were both associated with all-cause mortality in 1993-1994 with a lag of 1-day. NO_2, O_3 and CO were positively but more weakly associated with mortality than PM indices or SO_2. In the Bavarian region, neither TSP nor SO_2 was associated with mortality, but CO (at lag 1-day) and O_3 (at lag 0-day) were associated with all-cause mortality.	Total mortality excess deaths per 100 µg/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 µg/m^3 increase in TSP at lag 1-day, and 4.8 (0.7, 9.0) per 50 µg/m^3 increase in PM_{10}; and 1.4 (-0.5, 3.4) per 25 µg/m^3 $PM_{2.5}$.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (1997). +Rotterdam, the Netherlands, 1983-1991. TSP (median 42); BS (median 13).	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	5.5 (1.1, 9.9) per 100 $\mu g/m^3$ TSP at 1 day lag.
Kotěšovec et al. (2000). Northern Bohemia, Czech Republic, 1982-1994. TSP (121.3).	Total (excluding accidents and children younger than 1 yr), cause specific (cardiovascular and cancer), age (65 and less vs. otherwise), and gender specific mortality series were examined for their associations with TSP and SO_2 using logistic model, adjusting for seasonal cycles, influenza epidemics, linear and quadratic temperature terms. Lags 0 through 6 days, as well as a 7 day mean values were examined.	For the total mortality, TSP, but not SO_2, was associated. There were apparent differences in associations were found between men and women. For example, for age below 65 cardiovascular mortality was associated with TSP for men but not for women.	Total mortality percent excess deaths per 100 $\mu g/m^3$ increase in TSP at 2 day lag was 3.4 (0.5, 6.4).
Zanobetti et al. (2000a). Milan, Italy. 1980-1989. TSP mean = 142.	The focus of this study was to quantify mortality displacement using what they termed "GAM distributed lag models". (smoothing term was fited with Penalized Plines) Non-accidental total deaths were regressed on smooth function of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect.	TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45^{th} day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.	Total mortality percent increase estimates per IQR increase in TSP: 2.2 (1.4, 3.1) for single-day model; 6.7 (3.8, 9.6) for distributed lag model.
Anderson et al. (1996). London, UK, 1987-1992. BS (15)	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	Both O_3 (0 day lag) and BS (1 day lag) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	2.8% (1.4, 4.3) per 25 $\mu g/m^3$ BS at 1-d lag for total deaths. CVD (1 d) = 1.0 (-1.1, 3.1). Resp. (1 d) = 1.1 (-2.7, 5.0).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
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 μg/m^3 PM_{13} at 0 day lag.
Garcia-Aymerich et al. (2000). Barcelona, Spain. 1985-1989. Black Smoke no data distribution was reported).	Daily total (mean = 1.8/day), respiratory, and cardiovascular mortality counts of a cohort (9,987 people) with COPD or asthma were associated with black smoke (24-hr), SO_2 (24-hr and 1-hr max), NO_2 (24-hr and 1-hr max), O_3 (1-hr max), temperature, and relative humidity. Poisson GLM regression models using APHEA protocol were used. The resulting RRs were compared with those of the general population.	Daily mortality in COPD patients was associated with all six pollution indices. This association was stronger than in the general population only for daily 1-hr max of SO_2, daily 1-hr max and daily means of NO_2. BS and daily means of SO_2 showed similar or weaker associations for COPD patients than for the general population.	Total mortality percent increase per 25 μg/m^3 increase in avg. of 0-3 day lags of BS: 2.76 (1.31, 4.23) in general population, and 1.14 (-4.4, 6.98) in the COPD cohort.
Rahlenbeck and Kahl (1996). East Berlin, 1981-1989. "SP" (beta attenuation, 97)	Total mortality (as well as deviations from long-wave cycles) was regressed (OLS) on SP and SO_2, adjusting for day-of-week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 μg/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 μg/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 μg/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 μg/m^3 increase in 3-day average BS: 14.2 (1.6, 28.4) for all causes; 9.7 (-10.2, 34.1) for cardiovascular deaths; 23.2 (3.0, 47.4) for respiratory deaths.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Sunyer and Basagana (2001). Barcelona, Spain. 1990-1995. See Sunyer et al. (2000) for PM levels.	The analysis assessed any "independent" particle effects, after controlling for gaseous pollutants, on a cohort of patients with COPD (see the summary description for Sunyer et al. (2000) for analytical approach). PM_{10}, NO_2, O_3, and CO were analyzed.	PM_{10}, but not gaseous pollutants were associated with mortality for all causes. In the two-pollutant models, the PM_{10}-mortality associations were not diminished, whereas those with gaseous pollutants were.	Odds ratio for all cause mortality per IQR PM_{10} on the same-day (27 µg/m^3) was 11% (0, 24). In two pollutant models, the PM_{10} RRs were 10.5%, 12.9%, and 10.8% with NO_2, O_3, and CO, respectively.
Tobias and Campbell (1999). Barcelona, Spain. 1991-1995. Black Smoke (BS) (no data distribution was reported).	Study examined the sensitivity of estimated total mortality effects of BS to different approaches to modeling influenza epidemics: (1) with a single dummy variable; (2) with three dummy variables; (3) using daily number of cases of influenza. Poisson GLM regression used to model total daily mortality, adjusting for weather, long-term trend, and season, apparently following APHEA protocol.	Using the reported daily number of influenza cases resulted in a better fit (i.e., a lower AIC) than those using dummy variables. In the "better" model, the black smoke coefficient was about 10% smaller than those in the models with dummy influenza variables, but remained significant. Lags not reported.	Total mortality excess deaths per 25 µg/m^3 increase in BS: 1.37 (0.20, 2.56) for model using the daily case of influenza; 1.71 (0.53, 2.91) for model with three influenza dummy variables.
Alberdi Odriozola et al. (1998). Madrid, Spain, 1986-1992. "TSP" (beta attenuation, 47 for average of 2 stations)	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (1-day lag) and SO_2 (3-day lagged) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 µg/m^3 TSP at lag 1 day.
Díaz et al. (1999). Madrid, Spain. 1990-1992. TSP (no data distribution was reported).	Non-accidental, respiratory, and cardiovascular deaths (mean = 62.4, 6.3, and 23.8 per day, respectively). Auto-regressive Integrated Moving Average (ARIMA) models fit to both depend and independ. variables first to remove auto-correlation and seasonality (i.e., pre-whitening"), followed by examining cross-correlation to find optimal lags. Multivariate OLS models thus included ARIMA components, seasonal cycles (sine/cosine), V-shaped temp., and optimal lags found for pollution and weather variables. TSP, SO_2, NO_2, and O_3 examined. Season-specific analyses also conducted.	TSP was significantly associated with non-accidental mortality at lag 0 for year around and winter, but with a 1-day lag in summer. A similar pattern was seen for circulatory deaths. For respiratory mortality, a significant association with TSP was found only in summer (0-day lag). SO_2, NOx, and NO_2 showed similar associations with non-accidental deaths at lag 0 day. O_3' associations with non-accidental mortality was U-shaped, with inconsistent lags (1, 4, and 10).	For non-accidental mortality, excess deaths was 7.4% (confidence bands not reported; $p < 0.05$) per 100 µg/m^3 TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Wichmann et al., (2000) *Erfurt, Germany. 1995-1998. Number counts (NC) & mass concentrations (MC) of ultrafine particles in three size classes, 0.01 to 0.1 m, and fine particles in three size classes from 0.1 to 2.5 m diameter, using Spectrometryll Mobile Aerosol Spectrometry (MAS). MAS MC PM2.5-0.01 (mean 25.8, median 18.8, IQR 19.9). Filter measurements of PM_{10} (mean 38.2, median 31.0, IQR 27.7) and $PM_{2.5}$ (mean 26.3, median 20.2, IQR 18.5). MAS NC2.5-0.01 (mean 17,966 per cu.cm, median 14,769, IQR 13,269).	Total non-accidental, cardiovascular, and respiratory deaths (mean 4.88, 2.87, 1.08 per day, respectively) were related to particle mass concentration and number counts in each size class, and to mass concentrations of gaseous co-pollutants NO_2, CO, SO_2, using GAM regression models adjusted for temporal trends, day of week, weekly national influenza rates, temperature and relative humidity. Data analyzed by season, age group, and cause of death separately. Single-day lags and polynomial distributed lag models (PDL) used. Particle indices and pollutants fitted using linear, log-transformed, and LOESS transformations. Two-pollutant models with a particle index and a gaseous pollutant were fitted. The "best" model as used by Wichmann et al. (2000) was that having the highest t-statistic, since other criteria (e.g., log-likelihood for nested models) and AIC for non-nested models could not be applied due to different numbers of observations in each model. There should be little difference between these approaches and resulting differences in results should be small in practice. Sensitivity analyses included stratifying data by season, winter year, age, cause of death, or transformation of the pollution variable (none, logarithmic, non-parametric smooth).	Loss of stat. power by using a small city with a small number of deaths was offset by advantage of having good exposure representation from single monitoring site. Since ultrafine particles can coagulate into larger aggregates in a few hours, ultrafine particle size and numbers can increase into the fine particle category, resulting in some ambiguity. Significant associations were found between mortality and ultrafine particle number concentration (NC), ultrafine particle mass concentration (MC), fine particle mass concentration, or SO_2 concentration. The correlation between MC0.01-2.5 and NC0.01-0.1 is only moderate, suggesting it may be possible to partially separate effects of ultrafine and fine particles. The most predictive single-day effects are either immediate (lag 0 or 1) or delayed (lag 4 or 5 days), but cumulative effects characterized by PDL are larger than single-day effects. The significance of SO_2 is robust, but hard to explain as a true causal factor since its concentrations are very low. Age is an important modifying factor, with larger effects at ages < 70 than ≥ 70 years. Respiratory mortality has a higher RR than cardio-vascular mortality. A large number of models were fitted, with some significant findings of association between mortality and particle mass or number indices.	Total mortality excess deaths: Filter PM_{10} (0-4 d lag) = 6.6 (0.7, 12.8) per 50 µg/m^3. Filter $PM_{2.5}$ (0-1 d) = 3.0 (-1.7, 7.9). MC for $PM_{0.01-2.5}$ 6.2% (1.4, 11.2) for all year; by season, Winter = 9.2% (3.0, 15.7) Spring = 5.2% (-2.0, 12.8) Summer = -4.7% (-18.7, 11.7) Fall = 9.7% (1.9, 18.1) For ultrafine PM, NC 0.01-0.1 (0-4 d lag): All Year = 8.2% (0.3, 16.9) Winter = 9.7% (0.3, 19.9) Spring = 10.5% (-1.4, 23.9) Summer = -13.9% (-29.8, 5.7) Fall = 12.0% (2.1, 22.7) Best single-day lag: $PM_{0.01-0.1}$ per 25 µg/m^3: 3.6(-0.4, 7.7) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.9(0.0, 8.0) $PM_{2.5}$ per 25 µg/m^3: -4.0(-7.9, 0) PM_{10} per 25 µg/m^3: 6.4(0.3, 12.9)
Stolzel et al. (2003). Re-analysis of above study.	Re-analysis of above study using GAM with stringent convergence criteria as well as GLM/natural splines. The polynomial distributed lag model was not re-analyzed.	Very little change in PM risk coefficients when GAM models with stringent convergence criteria were used. When GLM./natural splines were used, many of the coefficients for number concentrations slightly increased, but the coefficients for mass concentrations decreased slightly.	Best single-day lag using GAM (stringent): $PM_{0.01-0.1}$ per 25 µg/m^3: 3.6(-0.4, 7.7) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.8(-0.1, 7.8) $PM_{2.5}$ per 25 µg/m^3: -4.0(-7.8, -0.1) PM_{10} per 25 µg/m^3: 6.2(0.1, 12.7) Best single-day lag using GLM/natural splines: $PM_{0.01-0.1}$ per 25 µg/m^3: 3.1(-1.6, 7.9) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.7(-0.9, 8.4) $PM_{2.5}$ per 25 µg/m^3: -3.4(-7.9, 1.4) PM_{10} per 25 µg/m^3: 5.3(-1.8, 12.9)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Zeghnoun et al. (2001). +Rouen and Le Havre, France. 1990-1995. PM_{13} mean = 32.9 for Rouen, 36.4 for Le Havre. BS mean = 18.7 for Rouen, 16.3 for Le Havre.	Total, cardiovascular, and respiratory mortality series were regressed on BS, PM_{13}, SO_2, NO_2, and O_3 in 1- and 2-pollutant models using GAM Poisson models adjusting for seasonal trends, day-of-week, and weather.	In Rouen, O_3, SO_2, and NO_2 were each significantly associated with total, respiratory, and cardiovascular mortality, respectively. In Le Havre, SO_2 and PM_{13} were associated with cardiovascular mortality. However, the lack of statistical significance reported for most of these results may be in part due to the relatively small population size of these cities (430,000 and 260,000, respectively).	PM_{13} total mortality RRs per IQR were 0.5% (-1.1, 2.1) in Rouen (IQR=20.6, 1-day lag) and 1.9% (-0.8, 7.4) in Le Havre (IQR=23.9, 1-day lag). BS total mortality RRs per IQR were 0.5% (-1.8, 2.9) in Rouen (IQR=14.2, 1-day lag) and 0.3% (-1.6, 2.2) in Le Havre (IQR=11.5, 0-1 day lag avg.).
Roemer and Van Wijnen (2001). + Amsterdam. 1987-1998. BS and PM_{10} means in "background" = 10 and 39; BS mean in "traffic" area = 21. (No PM_{10} measurements available at traffic sites)	Daily deaths for those who lived along roads with more than 10,000 motor vehicle, as well as deaths for total population, were analyzed using data from background and traffic monitors. Poisson GAM model was used adjusting for season, day-of-week, and weather. BS, PM_{10}, SO_2, NO_2, CO, and O3 were analyzed.	Correlations between the background monitors and traffic monitors were moderate for BS (r = 0.55) but higher for NO_2 (r = 0.79) and O_3 (r = 0.80). BS and NO_2 were associated with mortality in both total and traffic population. Estimated RR for traffic population using background sites was larger than the RR for total population using background sites. The RR for total pop. using traffic sites was smaller that RRs for total population using background sites. This is not surprising since the mean BS for traffic sites were larger that for background sites.	The RRs per 100 µg/m^3 BS (at lag 1-day) were 1.383 (1.153, 1.659), 1.887 (1.207, 2.949), and 1.122 (1.023, 1.231) for total population using background sites, traffic population using background sites, and total population using traffic sites, respectively. Results for traffic pop. using traffic sites not reported)
Anderson et al. (2001). +The west Midlands conurbation, UK. 1994-1996. PM means: PM_{10} = 23, $PM_{2.5}$ = 15, $PM_{10\text{-}2.5}$ = 9, BS = 13.2, sulfate = 3.7.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ (avg. lag 0 and 1 days) were 0.2% (-1.8, 2.2) per 24.4 uµg/m^3 PM_{10}, 0.6% (-1.5, 2.7) per 17.7 uµg/m^3 $PM_{2.5}$, and –0.6% (-4.2, 2.3) per 11.3 uµg/m^3 $PM_{10\text{-}2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
Keatinge and Donaldson (2001). Greater London, England, 1976-1995. BS mean = 17.7.	The study examined potential confounding effects of atypical cold weather on air pollution/mortality relationships. First, air pollution variables (SO_2, CO and BS) were modeled as a function of lagged weather variables These variables were deseasonalized by regressing on seine and cosine variables. Mortality regression (OLS) included various lagged and averaged weather and pollution variables. Analyses were conducted in the linear range of mortality/temperature relationship (15 to 0 degrees C).	Polluted days were found to be colder and less windy and rainy than usual. In the regression of mortality on the multiple-lagged temperature, wind, rain, humidity, sumshine, SO_2, CO, and BS, cold temperature was associated with mortality increase, but not SO_2 or CO. BS suggestive evidence, though not statistically significant, of association at 0- and 1-day lag.	3% (95% CI not reported) increase in daily mortality per 17.7 µg/m^3 of BS (lag 0 and 1).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America			
Cifuentes et al. (2000).+ Santiago, Chile. 1988-1996. $PM_{2.5}$ (64.0), and $PM_{10-2.5}$ (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. They also reported results for comparable GLM model.	Both PM size fractions associated with mortality, but different effects found for warmer and colder months. $PM_{2.5}$ and $PM_{10-2.5}$ 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 GAM models. In GLM models (whole year only), 1.4 (0.6, 2.1) for $PM_{2.5}$ and 1.6 (0.2, 3.0) for $PM_{10-2.5}$
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 model (only one non-parametric smoothing term), adjusting for temperature (average of 1-3 day lags) and seasonal cycles. Individual pollution lag days from 0 to 5, and average concentrations of previous 5 days were considered.	All three particle size fractions were associated individually with mortality. The effect size estimate was largest for $PM_{10-2.5}$. 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 (same model as above, with only one non-parametric smoothing term)	Excess infant mortality associated with $PM_{2.5}$, NO_2, and O_3 in the same average/lags. NO_2 and O_3 associations less consistent in multi-pollutant models.	Infant mortality excess risk: 18.2% (6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$ at avg. 3-5 lag days.
Borja-Aburto et al. (1998). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27)	Total, respiratory, cardiovascular, other deaths, and age-specific (age >= 65) deaths were related to $PM_{2.5}$, O_3, and NO_2, adjusting for 3-day lagged temperature and smoothing splines for temporal trend, using Poisson GAM model (only one non-parametric smoothing term).	$PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 avg.; 1-5 avg., respectively). $PM_{2.5}$ associations were most consistently significant. SO_2 was available, but not analyzed because of its "low" levels.	For total excess deaths, 3.4% (0.4, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$ for both 0 and 4 d lags. For respiratory (4 d) = 6.4 (-2.6, 16.2); for CVD (4 d) = 5.6 (-0.1, 11.5)
Borja-Aburto et al. (1997). Mexico-City, 1990-1992. TSP (median: 204)	Total, respiratory, cardiovascular, and age-specific (age > = 65) deaths were related to O_3, TSP, and CO, adjusting for minimum temperature (temperature also fitted seasonal cycles) using Poisson GLM models. The final models were estimated using the iteratively weighted and filtered least squares method to account for overdispersion and autocorrelation.	O_3, SO_2, and TSP were all associated with total mortality in separate models, but in multiple pollutant model, only TSP remained associated with mortality. CO association weak.	Total deaths: 6% (3.3, 8.3) per 100 $\mu g/m^3$ TSP at 0 d lag. CVD deaths: 5.2% (0.9, 9.9). Resp. deaths: 9.5% (1.3, 18.4).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America (cont'd)			
Tellez-Rojo et al. (2000). Mexico City. 1994. PM10 mean = 75.1.	One year of daily total respiratory and COPD mortality series were analyzed for their associations with PM_{10} and O3 using Poisson GLM model adjusting for cold or warm months, and 1-day lagged minimum temperature. The data were stratified by the place of deaths.	The average number of daily respiratory deaths, as well as that of COPD deaths, was similar for in and out of hospital. They found that the estimated PM_{10} relative risks were consistently larger for the deaths that occurred outside medical units. The results are apparently consistent with the assumption that the extent of exposure misclassification may be smaller for those who died outside medical units.	Percent excess for total respiratory and COPD mortality were 2.9% (0.9, 4.9) and 4.1% (1.3, 6.9) per 10 uµg/m^3 increase in 3-day lag PM_{10},
Pereira et al. (1998). Sao Paulo, Brazil, 1991-1992. PM_{10} (beta-attenuation, 65)	Intrauterine mortality associations with PM_{10}, NO_2, SO_2, CO, and O_3 investigated using Poisson GLM regression adjusting for season and weather. Ambient CO association with blood carboxyhemoglobin sampled from umbilical cords of non-smoking pregnant mothers studied in separate time period.	NO_2, SO_2, and CO were all individually significant predictor of the intrauterine mortality. NO_2 was most significant in multi-pollutant model. PM_{10} and O_3 were not significantly associated with the mortality. Ambient CO levels were associated with and carboxyhemoglobin of blood sampled from the umbilical cords.	Intrauterine mortality excess risk: 4.1% (-1.8, 10.4) per 50 µg/m^3 PM_{10} at 0 day lag.
Gouveia and Fletcher (2000). Sao Paulo, Brazil. 1991-1993. PM_{10} mean = 64.3.	All non-accidental causes, cardiovascular, and respiratory mortality were analyzed for their associations with air pollution (PM_{10}, SO_2, NO_2, O_3, and CO) using Poisson GLM model adjusting for trend, seasonal cycles, and weather. Potential roles of age and socio-economic status were examined by stratifying data by these factors.	There was an apparent effect modification by age categories. Estimated PM_{10} effects were higher for deaths above age 65 (highest for the age 85+ category), and no associations were found in age group < 65 years. Respiratory excess deaths were larger than those for cardiovascular or non-accidental deaths. Other pollutants were also associated with the elderly mortality.	Percent excess for total non-accidental, cardiovascular, and respiratory mortality for those with age > 65 were 3.3% (0.6, 6.0), 3.8% (0.1, 7.6), and 6.0 (0.5, 11.8), respectively, per 64.2 uµg/m^3 increase in PM_{10} (0-, 0-, and 1-day lag, respectively).
Conceição et al. (2001) +Sao Paulo, Brazil. 1994-1997. PM_{10} mean = 66.2	Daily respiratory deaths for children under 5 years of age were analyzed for their associations with air pollution (PM_{10}, SO_2, O_3, and CO) using GAM Poisson model adjusting for seasonal cycles and weather.	Significant mortality associations were found for CO, SO_2, and PM_{10} in single pollutant models. When all the pollutants were included, PM_{10} coefficient became negative and non-significant.	Percent excess for child (age < 5) respiratory deaths: 9.7% (1.5, 18.6) per 66.2 µg/m^3 PM_{10} (2-day lag) in single pollutant model.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Australia			
Morgan et al. (1998). Sydney, 1989-1993. Nephelometer (0.30 bscat/104m). Site-specific conversion: $PM_{2.5}$ 9; PM_{10} 18	Total, cardiovascular, and respiratory deaths were related to PM (nephelometer), O_3, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE model to adjust for autocorrelation.	PM, O_3, and NO_2 all showed significant associations with total mortality in single pollutant models. In multiple pollutant models, the PM and O_3 effect estimates for total and cardiovascular deaths were marginally reduced, but the PM effect estimate for respiratory deaths was substantially reduced.	4.7% (1.6, 8.0) per 25 µg/m^3 estimated $PM_{2.5}$ or 50 µg/m^3 estimated PM_{10} at avg. of 0 and 1 day lags. (Note: converted from nephelometry data)
Simpson et al. (1997). Brisbane, 1987-1993. PM_{10} (27, not used in analysis). Nephelometer (0.26 bscat/104m, size range: 0.01-2 m).	Total, cardiovascular, and respiratory deaths (also by age group) were related to PM (nephelometer), O_3, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE model to adjust for autocorrelation. Season-specific (warm and cold) analyses were also conducted.	Same-day PM and O_3 were associated most significantly with total deaths. The O_3 effect size estimates for cardiovascular and respiratory deaths were consistently positive (though not significant), and larger in summer. PM's effect size estimates were comparable for warm and cold season for cardiovascular deaths, but larger in warm season for respiratory deaths. NO_2 and SO_2 were not associated with mortality.	3.4% (0.4, 6.4) per 25 µg/m^3 1-h $PM_{2.5}$ increment at 0 d lag; and 7.8% (2.5, 13.2) per 25 µg/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 µg/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 µg/m^3 TSP at avg. of 0, 1, and 2 day lags.
Lee and Schwartz (1999). Seoul, Korea. 1991-1995. TSP mean = $9_{2.5}$.	Total deaths were analyzed for their association with TSP, SO_2, and O_3. A conditional logistic regression analysis with a case-crossover design was conducted. Three-day moving average values (current and two past days) of TSP and SO_2, and 1-hr max O_3 were analyzed separately. The control periods are 7 and 14 days before and/or after the case period. Both unidirectional and bi-directional controls (7 or 7 and 14 days) were examined, resulting in six sets of control selection schemes. Other covariates included temperature and relative humidity.	Among the six control periods, the two unidirectional retrospective control schemes resulted in odds ratios less than 1; the two unidirectional prospective control schemes resulted in larger odds ratios (e.g., 1.4 for 50 ppb increase in SO_2); and bi-directional control schemes resulted in odds ratios between those for uni-directional schemes. SO_2 was more significantly associated with mortality than TSP.	OR for non-accidental mortality per 100 µg/m^3 increase in 3-day average TSP was 1.010 (0.988, 1.032).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Xu et al. (2000). Shenyang, China, 1992. TSP (430).	Total (non-accidental), CVD, COPD, cancer and other deaths examined for their associations with TSP and SO_2,using Poisson (GAM, and Markov approach to adjust for mortality serial dependence) models, adjusting for seasonal cycles, Sunday indicator, quintiles of temp. and humidity. Ave. pollution values of concurrent and 3 preceding days used. While GAM models were used in the process, the risk estimates presented were for a fully parametric model (i.e., GLM).	Total deaths were associated with TSP and SO_2 in both single and two pollutant models. TSP was significantly associated with CVD deaths, but not with COPD. SO_2 significantly associated with COPD, but not with CVD deaths. Cancer deaths not associated with TSP or SO_2.	Percent total excess deaths per 100 μg/m^3 increase in 0-3 day ave. of TSP = 1.75 (0.65, 2.85); with SO_2 = 1.31 (0.14, 2.49) COPD TSP = 2.6 (-0.58, 5.89); with SO_2 = 0.76 (-2.46, 4.10). CVD TSP = 2.15 (0.56, 3.71); with SO_2 = 1.95 (1.19, 3.74). Cancer TSP = 0.87 (-1.14, 2.53); with SO_2 = 1.07 (-1.05, 3.23). Other deaths TSP = 3.52 (0.82, 6.30); with SO_2 = 2.40 (-0.51, 5.89).
Ostro et al. (1998). Bangkok, Thailand, 1992-1995 PM_{10} (beta attenuation, 65)	Total (non-accidental), cardiovascular, respiratory deaths examined for associations with PM_{10} (separate measurements showed 50% of PM_{10} was $PM_{2.5}$),using Poisson GAM model (only one non-parametric smoothing term in the model) adjusting for seasonal cycles, day-of-week, temp., humidity.	All the mortality series were associated with PM_{10} at various lags. The effects appear across all age groups. No other pollutants were examined.	Total mortality excess risk: 5.1% (2.1, 8.3) per 50 μg/m^3 PM_{10} at 3 d lag (0 and 2 d lags also significant). CVD (3 d ave.) = 8.3 (3.1, 13.8) Resp. (3 d ave.) = 3.0 (-8.4, 15.9)
Cropper et al. (1997). Delhi, India, 1991-1994 TSP (375)	Total (by age group), respiratory and CVD deaths related to TSP, SO_2, and NOx, using GEE Poisson model (to control for autocorrelation), adjusting for seasonal cycles (trigonometric terms), temperature, and humidity. 70% deaths occur before age 65 (in U.S., 70% occur after age 65).	TSP was significantly associated with all mortality series except with the very young (age 0-4) and the "very old" (age >= 65). The results were reported to be unaffected by addition of SO_2 to the model. The authors note that, because those who are affected are younger (than Western cities), more life-years are likely to be lost per person from air pollution impacts.	2.3% (significant at 0.05, but SE of estimate not reported) per 100 μg/m^3 TSP at 2 day lag.
Kwon et al. (2001) +Seoul, South Korea, 1994-1998. PM10 mean = 68.7.	The study was planned to test the hypothesis that patients with congestive heart failure are more susceptible to the harmful effects of ambient air pollution than the general population. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week, as well as the case-crossover design, with 7 and 14 days before and after the case period, were applied	The estimated effects were larger among the congestive heart failure patients than among the general population (2.5 ~ 4.1 times larger depending on the pollutants). The case-crossover analysis showed similar results. In two pollutant models, the PM_{10} effects were much lower when CO, NO_2, or SO_2 were included. O_3 had little impact on the effects of the other pollutants.	The RRs for PM_{10} (same-day) using the GAM approach for the general population and for the cohort with congestive heart failure were 1.4% (0.6, 2.2) and 5.8 (-1.1, 13.1), respectively, per 42.1 μg/m^3. Corresponding ORs using the case-crossover approach were 0.1% (-0.9, 1.2) and 7.4% (−2.2, 17.9), respectively.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Lee et al. (2000) +Seven major cities, Korea. 1991-1997. TSP mean = 77.9.	All non-accidental deaths were analyzed for their associations with TSP, SO_2, NO_2, O_3, and CO using GAM Poisson model adjusting for trend, seasonal cycles, and weather. Pollution relative risk estimates were obtained for each city, and then pooled.	In the results of pooled estimates for multiple pollutant models, the SO_2 relative risks were not affected by addition of other pollutants, whereas the relative risks for other pollutants, including TSP, were. The SO_2 levels in these Korean cities were much higher than the levels observed in the current U.S. For example, the 24-hr mean SO_2 levels in the Korean cities ranged from 12.1 to 31.4 ppb, whereas, in Samet et al.'s 20 largest U.S. cities, the range of 24-hr mean SO_2 levels were 0.7 to 12.8 ppb.	Percent excess deaths for all non-accidental deaths was 1.7% (0.8, 2.6) per 100 $\mu g/m^3$ 2-day moving average TSP.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

DRAFT-DO NOT QUOTE OR CITE

APPENDIX 8B

PARTICULATE MATTER-MORBIDITY STUDIES: SUMMARY TABLES

Appendix 8B.1: PM-Cardiovascular Admissions Studies

TABLE 8B-1. ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes. Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States			
Samet et al. (2000a,b) 14 US cities 1985-1994, but range of years varied by city PM_{10} ($\mu g/m^3$) mean, median, IQR: Birmingham, AL: 34.8, 30.6, 26.3 Boulder, CO: 24.4, 22.0, 14.0 Canton, OH: 28.4, 25.6, 15.3 Chicago, Il: 36.4, 32.6, 22.4 Colorado Springs, CO: 26.9, 22.9, 11.9 Detroit, MI: 36.8, 32.0, 28.2 Minneapolis/St. Paul, MN: 27.4, 24.1, 17.9 Nashville, TN: 31.6, 29.2, 17.9 New Haven, CT: 29.3h, 26.0, 20.2 Pittsburgh, PA: 36.0, 30.5, 27.4 Provo/Orem, UT: 38.9, 30.3, 22.8 Seattle, WA: 31.0, 26.7, 20.0 Spokane, WA: 45.3, 36.2, 33.5 Youngstown, OH: 33.1, 29.4, 18.6	Daily medicare hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Mean CVD counts ranged from 3 to 102/day in the 14 cities. Covariates: SO_2, NO_2, O_3, CO, temperature, relative humidity, barometric pressure. Stats: In first stage, performed city-specific, PM10-ONLY, generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 14 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and slopes of PM_{10} on co-pollutants.	City-specific risk estimates for a 10 $\mu g/m^3$ increase in PM_{10} ranged from -1.2% in Canton to 2.2% in Colorado Springs. Across-city weighted mean risk estimate was largest at lag 0, diminishing rapidly at other lags. Only the mean of lags 0 and 1 was significantly associated with CVD. There was no evidence of statistical heterogeniety in risk estimates across cities for CVD. City-specific risk estimates were not associated with the percent of the population that was non-white, living in poverty, college educated, nor unemployed. No evidence was observed that PM_{10} effects were modified by weather. No association was observed between the city-specific PM_{10} risk estimates and the city-specific correlation between PM_{10} and co-pollutants. However, due to the absence of multi-pollutant regression results, it is not clear whether this study demonstrates an independent effect of PM_{10}.	Percent Excess CVD Risk (95% CI), combined over cities per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d lag. 5.5% (4.7, 6.2) PM_{10}: 0–1d lag. 6.0% (5.1, 6.8) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d lag. 7.6% (6.0, 9.1)
Zanobetti and Schwartz (2003b)	Statistical reanalysis using GAM with improved convergence criterion (New GAM), GLM with natural splines (GLM NS), and GLM with penalized splines (GLM PS). Lag structure: average of lags 0 and 1.		Default GAM: 5.9% (5.1-6.7) New GAM: 4.95% (3.95-5.95) GLM NS: 4.8% (3.55-6.0) GLM PS: 5.0% (4.0-5.95)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Janssen et al. (2002) 14 U.S. cities studied in Samet et al. (2000a,b) above PM_{10} ($\mu g/m^3$) — Mean Summer/Winter — Ratio Birmingham 40.0/27.4 0.69 Boulder* 26.8/36.3 1.35 Canton 36.6/25.8 0.70 Chicago 42.5/30.4 0.71 Colorado Springs* 21.3/37.3 1.75 Detroit 42.8/32.8 0.77 Minneapolis 30.5/23.0 0.75 Nashville 40.1/31.9 0.80 New Haven 30.3/31.6 1.04 Pittsburgh 46.6/29.4 0.63 Seattle* 23.8/43.3 1.82 Spokane* 32.7/42.2 1.29 Provo-Urem* 31.4/66.3 2.11 Youngstown 40.7/30.1 0.74	Examined same database as Samet et al. (2000a,b) to evaluate whether differences in prevalence in air conditioning (AC) and/or the contribution of different sources to total PM_{10} emissions could partially explain the observed variability in exposure effect relations. Variables included 24-hr means of temperature. Cities were characterized and analyzed as either winter or nonwinter peaking. Rations between mean concentrations during summer (June, July August) and winter (January, February, March) were calculated. (*Winter peaking PM_{10} concentration.)	Analysis of city groups of winter peaking, PM_{10} and nonwinter peaking PM_{10} yielded coefficients for CVD-related hospitalization admissions that decreased significantly with increasing percentage of central AC for both city groups. Four source related variables coefficients for hospital admissions for CVD increased significantly with increasing percentage of PM_{10} from highway vehicles, highway diesels, oil combustion, metal processing, increasing population, and vehicle miles traveled (VMT) per sq mile and with decreasing percentage of PM_{10} from fugitive dust. For COPD and pneumonia association were less significant but the pattern of association were similar to that for CVD.	**Homes with AC** β CVD % change (SE) All cities −15.2 (14.8) Nonwinter peak cities −50.3** (17.4) Winter peak cities −51.7** (13.8) **Source PM_{10} from highway vehicles** % change (SE) β CVD 58.0* (9.9) [**p <0.05]
Zanobetti and Schwartz (2003b)	Statistical reanalysis of Janssen et al., 2002 findings using GLM with natural splines (GLM NS), and GLM with penalized splines (GLM PS). Lag structure: average of lags 0 and 1.	Zanobetti and Schwartz (2003b) reanalyzed the main findings from this study using alternative methods for controlling time and weather covariates. While the main conclusions of the study were not significantly altered, some changes in results are worth noting. The effect of air conditioning use on PM10 effect estimates was less pronounced and no longer statistically significant for the winter PM10-peaking cities using natural splines or penalized splines in comparison to the original Janssen et al. GAM analysis. The effect of air conditioning remained significant for the non-winter PM10-peaking cities. The significance of highway vehicles and diesels on PM10 effect sizes remained significant, as did oil combustion.	**Homes with AC** β CVD % change (SE) All cities GLM NS: −13.55 (14.9) GLM PS: -12.0 (14.1) Nonwinter peaking cities GLM NS: −44.1** (20.15) GLM PS: -38.4** (17.8) Winter peaking cities GLM NS: −6.1 (40.3) GLM PS: -41.5 (39.6) **Source PM_{10} from highway vehicles** % change (SE) β CVD GLM NS: 51.1** (14.7) GLM PS: 35.1** (14.3) [**p <0.05]

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Zanobetti et al. (2000b) 10 US cities 1986-1994 PM_{10} ($\mu g/m^3$) median, IQR: Canton, OH: 26, 15 Birmingham, AL: 31, 26 Chicago, Il: 33, 23 Colorado Springs, CO: 23, 13 Detroit, MI: 32, 28 Minneapolis/St. Paul, MN: 24, 18 New Haven, CT: 26, 21 Pittsburgh, PA: 30, 28 Seattle, WA: 27, 21 Spokane, WA: 36, 34	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Median CVD counts ranged from 3 to 103/day in the 10 cities. Covariates: SO_2, O_3, CO, temperature, relative humidity, barommetric pressure. Stats: In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 $\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. As with Samet et al. 2000., it is not clear whether this study demonstrates an independent effect of PM_{10}. This study used the old GAM model. Results have not been explicitly reanalyzed, but note that the 14 cities noted above in Zanobetti and Schwartz (2003b) include these 10 cities.	Percent Excess Risk (SE) combined over cities: Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d. 5.6 (4.7, 6.4) PM_{10}: 0–1 d. 6.2 (5.4, 7.0) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d. 7.8 (6.2, 9.4)
Schwartz (1999) 8 US metropolitan counties 1988-1990 median, IQR for PM_{10} ($\mu g/m^3$): Chicago, IL: 35, 23 Colorado Springs, CO: 23, 14 Minneapolis, MN: 28, 15 New Haven, CT: 37, 25 St. Paul, MN: 34, 23 Seattle, WA: 29, 20 Spokane, WA: 37, 33 Tacoma, WA: 37, 27	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Median daily hospitalizations: 110, 3, 14, 18, 9, 22, 6, 7, alphabetically by city. Covariates: CO, temperature, dewpoint temp. Stats: robust Poisson regression after removing admission outliers; generalized additive models with LOESS smooths for control of trends, seasons, and weather. Day of week dummy variables. Lag 0 used for all covariates.	In single-pollutant models, similar PM_{10} effect sizes obtained for each county. Five of eight county-specific effects were statistically significant, as was the PM_{10} effect pooled across locations. CO effects significant in six of eight counties. The PM_{10} and CO effects were both significant in a two pollutant model that was run for five counties where the PM_{10}/CO correlation was less than 0.5. Results reinforce those of Schwartz, 1997. This study used the old GAM model. No reanalysis has been reported.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0d. Individual counties: Chicago: 4.7 (2.6, 6.8) CO Spng: 5.6 (–6.8, 19.0) Minneap: 4.1 (–3.6, 12.5) New Hav: 5.8 (2.1, 9.7) St. Paul: 8.6 (2.9, 14.5) Seattle: 3.6 (–0.1, 7.4) Spokane: 6.7 (0.9, 12.8) Tacoma: 5.3 (3.1, 7.6) Pooled: 5.0 (3.7, 6.4) 3.8 (2.0, 5.5) w. CO

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Linn et al. (2000) Los Angeles 1992-1995 mean, SD: $PM_{10\ est}$ (μg/m^3): 45, 18	Hospital admissions for total cardiovascular diseases (CVD), congestive heart failure (CHF), myocardial infarction (MI), cardiac arrhythmia (CA) among all persons 30 years and older, and by sex, age, race, and season. Mean hospital admissions for CVD: 428. Covariates: CO, NO_2, O_3, temperature, rainfall. Daily gravimetric PM_{10} estimated by regression of every sixth day PM_{10} on daily real-time PM_{10} data collected by TEOM. Poisson regression with controls for seasons and day of week. Reported results for lag 0 only. Results reported as Poisson regression coefficients and their standard errors. The number of daily CVD admissions associated with the mean PM_{10} concentration can be computed by multiplying the PM_{10} coefficient by the PM_{10} mean and then exponentiating. Percent effects are calculated by dividing this result by the mean daily admission count for CVD.	In year-round, single-pollutant models, significant effects of CO, NO_2, and PM_{10} on CVD were reported. PM_{10} effects appeared larger in winter and fall than in spring and summer. No consistent differences in PM_{10} effects across sex, age, and race. CO risk was robust to including PM_{10} in the model; no results presented on PM_{10} robustness to co-pollutants. This study did not use the GAM model in developing its main findings.	% increase with PM_{10} change of 50 μg/m^3: $PM_{10\ est}$: 0 d. CVD ages 30+ 3.25% (2.04, 4.47) MI ages 30+ 3.04% (0.06, 6.12) CHF ages 30+ 2.02% (−0.94, 5.06) CA ages 30+ 1.01% (−1.93, 4.02)
Morris and Naumova (1998) Chicago, IL 1986-1989 mean, median, IQR, 75th percentile: PM_{10} (μg/m^3): 41, 38, 23, 51	Daily hospital admissions for congestive heart failure, CHF (ICD9 428), among persons over 65 years. Mean hospitalizations: 34/day. Covariates: O_3, NO_2, SO_2, CO, temperature, relative humidity. Gases measured at up to eight sites; daily PM_{10} measured at one site. Stats: GLM for time series data. Controlled for trends and cycles using dummy variables for day of week, month, and year. Residuals were modeled as negative binomial distribution. Lags of 0-3 days examined.	CO was only pollutant statistically significant in both single- and multi-pollutant models. Exposure misclassification may have been larger for PM_{10} due to single site. Results suggest effects of both CO and PM_{10} on congestive heart failure hospitalizations among elderly, but CO effects appear more robust. This study did not use the GAM model.	Percent Excess Risk (95% CI) per 50 μg/m^3 change in PM_{10}. PM_{10}: 0 d. 3.92% (1.02, 6.90) 1.96% (−1.4, 5.4) with 4 gaseous pollutants

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR μg/m^3	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Schwartz (1997) Tucson, AZ 1988-1990 mean, median, IQR: PM_{10} (μg/m^3): 42, 39, 23	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Mean hospitalizations: 13.4/day. Covariates: O_3, NO_2, CO, SO_2, temperature, dewpoint temperature. Gases measured at multiple sites; daily PM_{10} at one site. Stats: robust Poisson regression; generalized additive model with LOESS smooth for controlling trends and seasons, and regression splines to control weather. Lags of 0-2 days examined.	Both PM_{10} (lag 0) and CO significantly and independently associated with admissions, whereas other gases were not. Sensitivity analyses reinforced these basic results. Results suggest independent effects of both PM_{10} and CO for total cardiovascular hospitalizations among the elderly. This study used the old GAM model. No reanalysis has been reported.	Percent Excess Risk (95% CI) per 50 μg/m^3 change in PM_{10}. PM_{10}: 0 d. 6.07% (1.12, 1.27) 5.22% (0.17, 10.54) w. CO
Gwynn et al (2000) Buffalo, NY mn/max PM_{10} = 24.1/90.8 μg/m^3 SO_4^- = 2.4/3.9 H^+ = 36.4/38.2 nmol/m^3 CoH = 0.2/0.9 10^{-3} ft	Air pollution health effects associations with total, respiratory, and CVD hospital admissions (HA's) examined using Poisson model controlling for weather, seasonality, long-wave effects, day of week, holidays.	Positive, but non-significant assoc. found between all PM indices and circulatory hospital admissions. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. This study used the old GAM model. No reanalysis has been reported.	Percent excess CVD HA risks (95% CI) per PM_{10} = 50 μg/m^3; SO_4 = 15 μg/m^3; H^+ = 75 nmoles/m^3; COH = 0.5 units/1,000 ft: PM_{10} (lag 3) = 5.7% (−3.3, 15.5) SO_4 (lag 1) = 0.1% (−0.1, 0.4) H^+ (lag 0) = 1.9% (−0.3, 4.2) COH (lag 1) = 2.2% (−1.9, 6.3)
Lippmann et al. (2000) Detroit (Wayne County), MI 1992-1994 mean, median, IQR: $PM_{2.5}$ (μg/m^3): 18, 15, 11 PM_{10} (μg/m^3): 31, 28, 19 $PM_{10-2.5}$ (μg/m^3): 13, 12, 9	Various cardiovascular (CVD)-related hospital admissions (HA's) for persons 65+ yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For heart failure, all PM metrics yielded significant associations. Associations for IHD, dysrhythmia, and stroke were positive but generally non-sig. with all PM indices. Adding gaseous pollutants had negligible effects on various PM metric RR estimates. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per μg/m^3 in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity not usually present. However, small sample size limits power to distinguish between pollutant-specific effects.	Percent excess CVD HA risks (95% CI) per 50 μg/m^3 PM_{10}, 25 μg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$: IHD: $PM_{2.5}$ (lag 2) 4.3 (−1.4, 10.4) PM_{10} (lag 2) 8.9 (0.5, 18.0) $PM_{10-2.5}$ (lag 2) 10.5 (2.7, 18.9) Dysrhythmia: $PM_{2.5}$ (lag 1) 3.2 (−6.5, 14.0) PM_{10} (lag 1) 2.9 (−6.8, 13.7) $PM_{10-2.5}$ (lag 0) 0.2 (−12.2, 14.4) Heart Failure: $PM_{2.5}$ (lag 1) 9.1 (2.4, 16.2) PM_{10} (lag 0) 9.7 (0.2, 20.1) $PM_{10-2.5}$ (lag 0) 5.2 (−3.3, 14.5) Stroke: $PM_{2.5}$ (lag 0) 1.8 (−5.3, 9.4) PM_{10} (lag 1) 4.8 (−5.5, 16.2) $PM_{10-2.5}$ (lag 1) 4.9 (−4.7, 15.5)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Ito 2003 Detroit (Wayne County), MI	Statistical reanalysis using GAM with improved convergence criterion (New GAM), and GLM with natural splines (GLM NS). Same model structure as before.		IHD: New GAM: 8.0% (-0.3-17.1) GLM NS: 6.2% (-2.0-15.0) New GAM: 3.65% (-2.05-9.7)* GLM NS: 3.0% (-2.7-9.0)* New GAM: 10.2% (2.4-18.6)** GLM NS: 8.1% (0.4-16.4)** Dysrhythmias: New GAM: 2.8% (-10.9-18.7) GLM NS: 2.0% (-11.7-17.7) New GAM: 3.2% (-6.6-14.0)* GLM NS: 2.6% (-7.1-13.3)* New GAM: 0.1% (-12.4-14.4)** GLM NS: 0.0% (-12.5-14.3)** Heart Failure: New GAM: 9.2% (-0.3-19.6) GLM NS: 8.4% (-1.0-18.7) New GAM: 8.0% (1.4-15.0)* GLM NS: 6.8% (0.3-13.8)* New GAM: 4.4% (-4.0-13.5)** GLM NS: 4.9% (-3.55-14.1)**

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Moolgavkar (2000b) Three urban counties: Cook, IL; Los Angeles, CA; Maricopa, AZ. 1987-1995 Pollutant median, IQR: Cook: PM_{10}: 35, 22 LA: PM_{10}: 44, 26 $PM_{2.5}$: 22, 16 Maricopa: PM_{10}: 41, 19	Analysis of daily hospital admissions for total cardiovascular diseases, CVD, (ICD9 codes 390-429) and cerebrovascular diseases, CRD, (ICD9 430-448) among persons aged 65 and over. For Los Angeles, a second age group, 20-64, was also analyzed. Median daily CVD admissions were 110, 172, and 33 in Cook, LA, and Maricopa counties, respectively. PM_{10} available only every sixth day in LA and Maricopa counties. In LA, every-sixth-day $PM_{2.5}$ also was available. Covariates: CO, NO_2, O_3, SO_2, temperature, relative humidity. Stats: generalized additive Poisson regression, with controls for day of week and smooth temporal variability. Single-pollutant models estimated for individual lags from 0 to 5. Two-pollutant models also estimated, with both pollutants at same lag.	In single-pollutant models in Cook and LA counties, PM was significantly associated with CVD admissions at lags 0, 1, and 2, with diminishing effects over lags. $PM_{2.5}$ also was significant in LA for lags 0 and 1. For the 20-64 year old age group in LA, risk estimates were similar to those for 65+. In Maricopa county, no positive PM_{10} associations were observed at any lag. In two-pollutant models in Cook and LA counties, the PM_{10}/$PM_{2.5}$ risk estimates diminished and/or were rendered non-significant. Little evidence observed for associations between CRD admissions and PM. These results suggest that PM is not independently associated with CVD or CRD hospital admissions.	Percent Excess CVD Risk (95% CI) Effects computed for 50 µg/m^3 change in PM_{10} and 25 µg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Moolgavkar (2003)	Statistical reanalysis using GAM with improved convergence criterion (New GAM), and GLM with natural splines (GLM NS). New analyses were run with variable and in some cases more extensive control of time than in original analysis.		Cook County, IL: New GAM100df: 4.05% (2.9-5.2) GLM NS100df: 4.25% (3.0-5.5) Los Angeles County, CA: New GAM30df: 3.35% (1.2-5.5) New GAM100df: 2.7% (0.6-4.8) GLM NS100df: 2.75% (0.1-5.4) New GAM30df: 3.95% (2.2-5.7)* New GAM100df: 2.9% (1.2-4.6)* GLM nspline100df: 3.15% (1.1-5.2)*
Zanobetti et al. (2000a) Cook County, IL 1985-1994 Median, IQR: PM_{10} ($\mu g/m^3$): 33, 23	Total cardivascular hospital admissions in persons 65 and older (ICD 9 codes390-429) in relation to PM_{10}. Data were analyzed to examine effect modification by concurrent or preexisting cardiac and/or respiratory conditions, age, race, and sex. No co-pollutants included.	Evidence seen for increased CVD effects among persons with concurrent respiratory infections or with previous admissions for conduction disorders.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ PM_{10}, 0-1 D. AVG. CVD: 6.6 (4.9-8.3)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} ($\mu g/m^3$): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} ($\mu g/m^3$): 29.1, 27.6, 12.0 $PM_{2.5}$ ($\mu g/m^3$): 19.4, 17.5, 9.35 CP ($\mu g/m^3$): 9.39, 8.95, 4.52 10-100 nm PM counts ($count/cm^3$): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals ($\mu g/m^3$): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates ($\mu g/m^3$): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity ($\mu g/m^3$): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM ($\mu g/m^3$): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon ($\mu g/m^3$): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for dysrhythmias, DYS, (ICD 9 code 427) and all cardiovascular diseases, CVD, (codes 402, 410-414, 427, 428, 433-437, 440, 444, 451-453) for persons aged 16 and older in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all CVD in period 1 were 6.5 and 28.4, respectively. Mean daily ED visits for dysrhythmias and all CVD in period 2 were 11.2 and 45.1, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day of week and hospital entry/exit indicators also included. Pollutants were treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, significant negative association (p=0.02) observed between CVD and 3-day average PM_{10}. There was ca. 2% drop in CVD per 10 $\mu g/m^3$ increase in PM_{10}. CVD was positively associated with NO_2 (p=0.11) and negatively associated with SO_2 (p=0.10). No association observed between dysrhythmias and PM_{10} in period 1. However, dysrhythmias were positively associated with NO_2 (p=0.06). In period 2, i.e., the first year of operation of the superstation, no associations seen with PM_{10} or $PM_{2.5}$. However, significant positive associations observed between CVD and elemental carbon (p=0.005) and organic matter (p=0.02), as well as with CO (p=0.001). For dysrhythmias, significant positive associations observed with elemental carbon (p=0.004), CP (p=0.04), and CO (p=0.005). These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Percent Excess Risk (p-value): Effects computed for 50 $\mu g/m^3$ change in PM_{10}; 25 $\mu g/m^3$ for CP and $PM_{2.5}$; 25,000 $counts/cm^3$ for 10-100 nm counts. Period 1: PM_{10}, 0-2 d. avg. CVD: −8.2 (0.02) DYS: 4.6 (0.58) Period 2: 0-2 d. avg. in all cases CVD % effect; DYS % effect: PM_{10}: 5.1 (−7.9, 19.9); 13.1 (−14.1, 50.0) $PM_{2.5}$: 6.1 (−3.1, 16.2); 6.1 (−12.6, 28.9) CP: 17.6 (−4.6, 45.0); 53.2 (2.1, 129.6) 10-100 nm counts: −11.0 (0.17); 3.0 (0.87)

DRAFT-DO NOT QUOTE OR CITE

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)

DRAFT-DO NOT QUOTE OR CITE

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

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} (μg/m^3): 18, 16, 10 CP_{est} (μg/m^3): 12, 10, 8 $PM_{10\ est}$ (μg/m^3): 30, 27, 15	Daily hospitalizations for dysrhythmias, DYS (ICD9 code 427; mean 5/day); heart failure, HF (428; 9/d); ischemic heart disease, IHD (410-414; 24/d); cerebral vascular disease, CVD (430-438; 10/d); and diseases of the peripheral circulation, DPC (440-459; 5/d) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were estimated, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models used and non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in cardiac outcome (DVS, HF, IHD). No associations with vascular outcomes, except for CPest with DPC. In multi-pollutant models, PM effects estimates reduced by variable amounts (often >50%) for specific endpoints and no statistically significant (at $p<0.05$) PM associations seen with any cardiac or circulatory outcome (results not shown). Use of estimated PM metrics limits interpretation of pollutant-specific results. However, results suggest that linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when full range of gaseous pollutants also modeled.	Single pollutant models: Percent excess risk (95% CI) per 50 μg/m^3 PM_{10}; 25 μg/m^3 $PM_{2.5}$; and 25 μg/m^3 $PM_{10-2.5}$. All cardiac HA (lags 2-5 d): $PM_{2.5}$ 1-poll = 8.1 (2.45, 14.1) $PM_{2.5}$ w/4 gases = −1.6 (−10.4, 8.2); w/CO = 4.60 (−3.39, 13.26) PM_{10} 1-poll = 12.07 (1.43, 23.81) w/4 gases = −1.40 (−12.53, 11.16) w/CO = 10.93 (0.11, 22.92) $PM_{10-2.5}$ 1-poll = 20.46 (8.24, 34.06) w/4 gases = 12.14 (−1.89, 28.2); w/CO = 19.85 (7.19, 34.0) DYS: FP_{est} (0 d): 6.1 (1.9, 10.4) CP_{est} (0 d): 5.2 (−0.21, 1.08) $PM_{10\ est}$: (0 d): 8.41 (2.89, 14.2) HF: FP_{est} (0−2 d): 6.59 (2.50, 10.8) CP_{est} (0−2 d): 7.9 (2.28, 13) $PM_{10\ est}$ (0−2 d): 9.7 (4.2, 15.5) IHD: FP_{est} (0−2 d): 8.1 (5.4, 10.8) CP_{est} (0 d): 3.7 (1.3, 6.3) $PM_{10\ est}$ (0−1 d): 8.4 (5.3, 11.5)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 **HOSPITAL ADMISSIONS** H+ ($nmol/m^3$): 25.7, 36.8 Sulfate ($nmol/m^3$): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for angina/myocardial infarction (mean 1.8/day), congestive heart failure (1.0/day), dysrhythmia/conduction disturbance (0.8/day), and all cardiac conditions (3.5/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations observed between all cardiac ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations observed with H+, sulfate, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics were significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions. In cause-specific, single-pollutant models, PM tended to be positively associated with dysrhythmia/conductive disturbances but negatively associated with congestive heart failure (no quantitative results presented). The objective decision rule used for selecting lags reduced the risk of data mining; however, the biological plausibility of lag effects beyond 3-5 days is open to question. Rich co-pollutant data base. Results imply no effects of PM independent of co-pollutants.	Percent Excess Risk (p-value) computed for 50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ and mean levels of sulfate and COH. Full year results for all cardiac conditions, single pollutant models: PM_{10}: 3d. 29.3 (P=0.003) $PM_{2.5}$: 3d. 14.4 (P=0.055) H+: 4–9 d. avg. –1.8 (0.010) Sulfate: 4d. –6.0 (0.001) COH max: 7d. –5.4 (0.027) Full year results for all cardiac conditions, multi-pollutant models: No significant PM associations.

DRAFT-DO NOT QUOTE OR CITE

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} µg/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 µg/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. (1999b) Greater London, England 1992-1994 Pollutant: mean, median, 90-10 percentile range: PM_{10} (µg/m^3): 28.5, 24.8, 30.7 Black Smoke (µg/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 µg/m^3 PM_{10} and 25 µg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh, Scotland 1981-1995 (BS and SO_2) 1992-1995 (PM_{10}, NO_2, O_3, CO) Means for long and short series: BS: 12.3, 8.7 PM_{10}: NA, 20.7	Daily emergency hospital admissions for cardiovascular disease (ICD9 codes 410-414, 426-429, 434-440) for persons less than 65 years and for persons 65 or older. Separate analyses presented for long (1981-1995) and short (1992-1995) series. Mean hospital admissions for long and short series: <65, 3.5, 3.4; 65+, 8.0, 8.7. Covariates: SO_2, NO_2, O_3, CO, wind speed, temperature, rainfall. PM_{10} measured by TEOM. Stats: Poisson log-linear regression; trend and seasons controlled by monthly dummy variables over entire series; day of week dummy variables; min daily temperature modeled using octile dummies. Pollutants expressed as cumulative lag 1-3 day moving avg.	In long series, neither BS nor NO_2 were associated with CVD admissions in either age group. In the short series, only 3-day moving average PM_{10} was positively and significantly associated with CVD admissions in single-pollutant models, and only for persons 65 or older. BS, SO_2, and CO also showed positive associations in this subset, but were not significant at the 0.05 level. The PM_{10} effect remained largely unchanged when all other pollutants were added to the model, however quantitative results were not given. Results appear to show an effect of PM_{10} independent of co-pollutants.	Percent Excess Risk (95% CI): Effects computed for 50 μg/m³ change in PM_{10} and 25 μg/m³ change in BS. Long series: BS, 1–3 d. avg. <65: –0.5 (–5.4, 4.6) 65+: –0.5 (–3.8, 2.9) Short series: BS, 1–3 d. avg. <65: –9.5 (–24.6, 8.0) 65+: 5.8 (–4.9, 17.8) PM_{10}, 1–3 d. avg. <65: 2.0 (–12.5, 19.0) 65+: 12.4 (4.6, 20.9)
Wordley et al. (1997) Birmingham, UK 4/1/92-3/31/94 mean, min, max: PM_{10} (μg/m³): 26, 3, 131	Daily hospital admissions for acute ischemic heart disease (ICD9 codes 410-429) for all ages. Mean hospitalizations: 25.6/day. Covariates: temperature and relative humidity. Stats: Linear regression with day of week and monthly dummy variables, linear trend term. Lags of 0-3 considered, as well as the mean of lags 0-2.	No statistically significant effects observed for PM_{10} on ischemic heart disease admissions for any lag. Note that PM_{10} was associated with respiratory admissions and with cardiovascular mortality in the same study (results not shown here).	% change (95% CI) per 50 μg/m³ change PM_{10} IHD admissions: PM_{10} 0-d lag: 1.4% (–4.4, 7.2) PM_{10} 1-d lag: –1.3% (–7.1, 4.4)
Díaz et al. (1999) Madrid, Spain 1994-1996 TSP by beta attenuation Summary statistics not given.	Daily emergency hospital admissions for all cardiovascular causes (ICD9 codes 390-459) for the Gregorio Maranon University Teaching Hospital. Mean admissions: 9.8/day. Covariates: SO_2, NO_2, O_3, temperature, pressure, relative humidity, excess sunlight. Stats: Box-Jenkins time-series methods used to remove autocorrelations, followed by cross-correlation analysis; sine and cosine terms for seasonality; details unclear.	No significant effects of TSP on CVD reported.	No quantitative results presented for PM.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Australia			
Morgan et al. (1998) Sydney, Australia 1990-1994 mean, median, IQR, 90-10 percentile range: Daily avg. bscat/10^4m: 0.32, 0.26, 0.23, 0.48 Daily max 1-hr bscat/10^4m: 0.76, 0.57, 60, 1.23	Daily hospital admissions for heart disease (ICD9 codes 410, 413, 427, 428) for all ages, and separately for persons less than 65 and persons 65 or greater. Mean daily admissions: all ages, 47.2; <65, 15.4; 65+, 31.8. PM measured by nephelometry (i.e., light scattering), which is closely associated with $PM_{2.5}$. Authors give conversion for Sydney as $PM_{2.5}$ =30 × bscat. Covariates: O_3, NO_2, temperature, dewpoint temperature. Stats: Poisson regression; trend and seasons controlled with linear time trend and monthly dummies; temperature and dewpoint controlled with dummies for eight levels of each variable; day of week and holiday dummies. Single and cumulative lags from 0-2 considered. Both single and multi-pollutant models were examined.	In single-pollutant models, NO_2 was strongly associated with heart disease admissions in all age groups. PM was more weakly, but still significantly associated with admissions for all ages and for persons 65+. The NO_2 association in the 65+ age group was unchanged in the multi-pollutant model, whereas the PM effect disappeared when NO_2 and O_3 were added to the model.. These results suggest that PM is not robustly associated with heart disease admissions when NO_2 is included, similar to the sensitivity of PM to CO in other studies.	Percent Excess Risk (95% CI): Effects computed for 25 µg/m^3 $PM_{2.5}$ (converted from bscat). 24-hr avg. $PM_{2.5}$ 0 d. <65: 1.8 (−2.9, 6.7) 65+: 4.9 (1.6, 8.4) All: 3.9 (1.1, 6.8) 24-hr $PM_{2.5}$, 0 d w. NO_2 and O_3. 65+: 0.12 (−1.3, 1.6) 1-hr $PM_{2.5}$, 0 d. <65: 0.19 (−1.6, 2.0) 65+: 1.8 (0.5, 3.2) All: 1.3 (0.3, 2.3)
Asia			
Wong et al. (1999a) Hong Kong 1994-1995 median, IQR for PM_{10} (µg/m^3): 45.0, 34.8	Daily emergency hospital admissions for cardiovascular diseases, CVD (ICD9 codes 410-417, 420-438, 440-444), heart failure, HF (ICD9 428), and ischemic heart disease, IHD (ICD9 410-414) among all ages and in the age categories 5-64, and 65+. Median daily CVD admissions for all ages: 101. Covariates: NO_2, O_3, SO_2, temperature, relative humidity. PM_{10} measured by TEOM. Stats: Poisson regression using the APHEA protocol; linear and quadratic control of trends; sine and cosine control for seasonality; holiday and day of week dummies; autoregressive terms. Single and cumulative lags from 0-5 days considered.	In single-pollutant models, PM_{10}, NO_2, SO_2, and O_3 all significantly associated with CVD admissions for all ages and for those 65+. No multi-pollutant risk coefficients were presented; however, the PM_{10} effect was larger when O_3 was elevated (i.e., above median). A much larger PM_{10} effect was observed for HF than for CVD or IHD. These results confirm the presence of PM_{10} associations with cardiovascular admissions in single-pollutant models, but do not address the independent role of PM_{10}.	Percent Excess Risk (95% CI): Effects computed for 50 µg/m^3 change in PM_{10}. PM_{10}, 0–2 d. avg. CVD: 5–64: 2.5 (−1.5, 6.7) 65+: 4.1 (1.3, 6.9) All: 3.0 (0.8, 5.4) HF (PM_{10}, 0-3 d ave.): All: 26.4 (17.1, 36.4) IHD (PM_{10}, 0-3 d ave.): All: 3.5 (−0.5, 7.7)

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.2. PM-Respiratory Hospitalization Studies

TABLE 8B-2. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Samet et al, (2000a,b)* Study Period: 84- 95 14 U.S. Cities: Birmingham, Boulder, Canton, Chicago, Col. Springs, Detroit, Minn./St. Paul, Nashville, New Haven, Pittsburgh, Provo/Orem, Seattle, Spokane, Youngstown. Mean pop. aged 65+ yr per city =143,000 PM_{10} mean = 32.9 µg/m^3 PM_{10} IQR = NR	Hospital admissions for adults 65+ yrs. for CVD (mean=22.1/day/city), COPD (mean=2.0/day/city), and Pneumonia (mean=5.6/day/city) related to PM_{10}, SO_2, O_3, NO_2, and CO. City-specific Poisson models used with adjustment for season, mean temperature (T) and relative humidity (RH) (but not their interaction), as well as barometric pressure (BP) using LOESS smoothers (span usually 0.5). Indicators for day-of-week and autoregressive terms also included.	PM_{10} positively associated with all three hospital admission categories, but city specific results ranged widely, with less variation for outcomes with higher daily counts. PM_{10} effect estimates not found to vary with co-pollutant correlation, indicating that results appear quite stable when controlling for confounding by gaseous pollutants. Analyses found little evidence that key socioeconomic factors such as poverty or race are modifiers, but it is noted that baseline risks may differ, yielding differing impacts for a given RR.	PM_{10} = 50 µg/m^3 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)
Reanalysis of Samet et al (2000) by Zanobetti and Schwartz (2003b)	Re-analyses of Samet et al. (2000) with more stringent GAM convergence criteria and alternative models.	Results differ somewhat from original analyses, especially for pneumonia. Results indicate that the stricter convergence criteria results in about a 14% lower GAM effect than in the originally published analyses method. Authors recommend the penalized spline model results.	COPD 2 day mean (lag 0, lag1): Default GAM ER=9.4 (5.9, 12.9) Strict GAM ER = 8.8 (4.8, 13.0) NS GLM ER=6.8 (2.8, 10.8) PS GLM ER = 8.0 (4.3, 11.9) Pneumonia 2 day mean (lag 0, lag1): Default GAM ER=9.9 (7.4, 12.4) Strict GAM ER =8.8(5.9, 11.8) NS GLM ER=2.9 (0.2,5.6) PS GLM ER = 6.3 (2.5,10.3)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Zanobetti et al. (2000b)+ 10 U.S. Cities	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular and respiratory disease in persons aged 65 yr. Covariates: SO_2, O_3, CO, temperature, relative humidity, barometric pressure. In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 d considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 $\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. Suggests association between PM_{10} and total respiratory hospital admissions among the elderly.	Percent excess respiratory risk (95% CI) per 50 $\mu g/m^3$ PM_{10} increase: COPD (0-1 d lag) = 10.6 (7.9, 13.4) COPD (unconstrained dist. lag) = 13.4 (9.4, 17.4) Pneumonia (0-1 d lag) = 8.1 (6.5, 9.7) Pneumonia (unconstrained dist. lag) = 10.1 (7.7, 12.6)
Jamason et al. (1997) New York City, NY (82 - 92) Population = NR PM_{10} mean = 38.6 $\mu g/m^3$	Weather/asthma relationships examined using a synoptic climatological multivariate methodology. Procedure relates homogenous air masses to daily counts of overnight asthma hospital admission.	Air pollution reported to have little role in asthma variations during fall and winter. During spring and summer, however, the high risk categories are associated with high concentration of various pollutants (i.e., PM_{10}, SO_2,NO_2, O_3).	NR
Chen et al. (2000)+ Reno-Sparks, NV (90 - 94) Population = 307,000 B-Gauge PM_{10} mean=36.5 $\mu g/m^3$ PM_{10} IQR = 18.3-44.9 $\mu g/m^3$ PM_{10} maximum = 201.3 $\mu g/m^3$	Log of COPD (mean=1.72/day) and gastroenteritis (control) admissions from 3 hospitals analyzed using GAM regression, adjusting for effects of day-of-week, seasons, weather effects (T, WS), and long-wave effects. Only one LOESS used with GAM, so the default convergence criteria may be satisfactory in this case. No co-pollutants considered.	PM_{10} positively associated with COPD admissions, but no association with gastroenteritis (GE) diseases, indicating biologically plausible specificity of the PM_{10}-health effects association. Association remained even after excluding days with PM_{10} above 150 $\mu g/m^3$.	<u>COPD All age Admissions</u> 50 $\mu g/m^3$ IQR PM_{10} (single pollutant): ER = 9.4% (CI: 2.2, 17.1)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Gwynn et al. (2000)+ Buffalo, NY (5/88-10/90) PM_{10} mn./max. = 24.1/90.8 µg/m^3 PM_{10} IQR = 14.8-29.2 µg/m^3 $SO_4^=$ mn./max. = 2.4/3.9 µg/m^3 $SO_4^=$ IQR = 23.5 – 7.5 µg/m^3 H^+ mn/max = 36.4/382 nmol/m^3 H^+ IQR = 15.7-42.2 nmol/m^3 CoH mn/max = 0.2/0.9 10 3 ft. CoH IQR = 0.1-0.3	Air pollutant-health effect associations with total, respiratory, and circulatory hospital admissions and mortality examined using Poisson methods controlling for weather, seasonality, long-wave effects, day of week, and holidays using GAM with LOESS terms.	Strongest associations found between $SO_4^=$ and respiratory hospital admissions, while secondary aerosol H^+ and $SO_4^=$ demonstrated the most coherent associations across both respiratory hospital admissions and mortality. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. CoH weakness in associations may reflect higher toxicity by acidic sulfur containing secondary particles versus carbonaceous primary particles.	<u>Respiratory Hospital Admissions(all ages) PM Index (using standardized conc. increment)</u> -Single Pollutant Models For PM_{10} = 50 µg/m^3; SO_4 = 15 µg/m^3; H^+ = 75nmoles/m^3;COH = 0.5 units/1000ft PM_{10}(lag 0) ER = 11% (CI: 4.0, 18) $SO_4^=$(lag 0) ER = 8.2% (CI: 4.1, 12.4) H^+(lag 0) ER = 6% (CI: 2.8, 9.3) CoH(lag0) ER = 3% (CI: -1.2, 7.4)
Gwynn and Thurston (2001)+ New York City, NY 1988, 89, 90 PM_{10} 37.4 µg/m^3 mean	Respiratory hospital admissions, race specific for PM_{10}, H^+, O_3, $SO_4^=$. LOESS GAM regression model used to model daily variation in respiratory hospital admissions, day-week, seasonal, and weather aspects addressed in modeling.	Greatest difference between the white and non-white subgroups was observed for O_3. However, within race analyses by insurable coverage suggested that most of the higher effects of air pollution found for minorities were related to socio-economic studies.	PM_{10} (max-min) increment 1 day lag white 1.027 (0.971-1.074) non-white (1.027 (0.988-1.069)
Jacobs et al. (1997) Butte County, CA (83 - 92) Population = 182,000 PM_{10} mean = 34.3 µg/m^3 PM_{10} min/max = 6.6 / 636 µg/m^3 CoH mean = 2.36 per 1000 lin. ft. CoH min/max = 0 / 16.5	Association between daily asthma HA's (mean = 0.65/day) and rice burning using Poisson GLM with a linear term for temperature, and indicator variables for season and yearly population. Co-pollutants were O_3 and CO. PM_{10} estimated for 5 of every 6 days from CoH.	Increases in rice straw burn acreage found to correlate with asthma HA's over time. All air quality parameters gave small positive elevations in RR. PM_{10} showed the largest increase in admission risk.	Asthma HA's (all ages) For an increase of 50 µg/m^3 PM_{10}: ER = 6.11% (not statistically significant)
Linn et al. (2000) Los Angeles, CA (92 - 95) Population = NR PM_{10} mean = 45.5 µg/m^3 PM_{10} Min/Max = 5/132 µg/m^3	Pulmonary hospital admissions (HA's) (mean=74/day) related to CO, NO_2, PM_{10}, and O_3 in Los Angeles using GLM Poisson model with long-wave spline, day of week, holidays, and weather controls.	PM_{10} positively associated with pulmonary admissions year-round, especially in winter. No association with cerebro-vascular or abdominal control diseases. However, use of linear temperature, and with no RH interaction, may have biased effect estimates downwards for pollutants here most linearly related to temperature (i.e., O_3 and PM_{10}).	<u>Pulmonary HA's (>29 yrs.)</u> PM_{10} = 50 µg/m^3 (Lag 0)ER = 3.3% (CI: 1.7, 5)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Moolgavkar et al. (1997)+ Minneapolis-St. Paul 86 - 91 Population.= NR Birmingham, AL '86-'91 Population. = NR PM_{10} mean = 34 µg/m^3 (M-SP) PM_{10} IQR =22-41 µg/m^3 (M-SP) PM_{10} mean =43.4 µg/m^3(Birm) PM_{10} IQR =26-56 µg/m^3(Birm)	Investigated associations between air pollution (PM_{10}, SO_2, NO_2 O_3, and CO) and hospital admissions for COPD (mean/day=2.9 in M-SP; 2.3 in Birm) and pneumonia (mean=7.6 in M-SP; 6.0 in Birm) among older adults (>64 yrs.). Poisson GAM's used, controlling for day-of-week, season, LOESS of temperature (but neither RH effects nor T-RH interaction considered).	In the M-SP area, PM_{10} significantly and positively associated with total daily COPD and pneumonia admissions among elderly, even after simultaneous inclusion of O_3. When four pollutants included in the model (PM_{10}, SO_2, O_3, NO_2), all pollutants remained positively associated. In Birm., neither PM_{10} nor O_3 showed consistent associations across lags. The lower power (fewer counts) and lack of T-RH interaction weather modeling in this Southern city vs. M-SP may have contributed to the differences seen between cities.	<u>COPD + Pneumonia Admissions (>64yrs.)</u> In M-SP, For PM_{10} = 50 µg/m^3 (max lg) ER(lg 1) = 8.7% (CI: 4.6, 13) With O_3 included simultaneously: ER(lg1)= 6.9% (95 CI: 2.7, 11.3) In Birm, For PM_{10}=50 µg/m^3 (max lg.) ER(lg 0) = 1.5% (CI: -1.5, 4.6) With O_3 included simultaneously: ER(lg0) = 3.2% (CI: -0.7, 7.2)
Nauenberg and Basu (1999) Los Angeles (91 - 94) Wet Season = 11/1-3/1 Dry Season = 5/1-8/15 Population .= 2.36 Million PM_{10} Mean = 44.81 µg/m^3 PM_{10} SE = 17.23 µg/m^3	The effect of insurance status on the association between asthma-related hospital admissions and exposure to PM_{10} and O_3 analyzed, using GLM Poisson regression techniques with same day and 8-day weighted moving average levels, after removing trends using Fourier series. Compared results during wet season for all asthma HA's (mean = 8.7/d), for the uninsured (mean=0.77/d), for MediCal (poor) patients (mean = 4.36/d), and for those with other private health or government insurance (mean = 3.62/d).	No associations found between asthma admissions and O_3. No O_3 or PM_{10} associations found in dry season. PM_{10} averaged over eight days associated with increase in asthma admissions, with even stronger increase among MediCal asthma admissions in wet season. The authors conclude that low income is useful predictor of increased asthma exacerbations associated with air pollution. Non-respiratory HA's showed no such association with PM_{10}.	<u>All Age Asthma HA's</u> PM_{10} = 50 µg/m^3, no co-pollutant, during wet season (Jan. 1 - Mar. 1): <u>All Asthma Hospital Admissions</u> 0-d lag PM_{10} ER = 16.2 (CI: 2.0, 30) 8-d avg. PM_{10} ER = 20.0 (CI: 5.3, 35) <u>MediCal Asthma Hospital Admissions</u> 8-d avg. PM_{10} ER = 13.7 (3.9, 23.4) <u>Other Insurance Asthma HA's</u> 8-d avg. PM_{10} ER = 6.2 (-3.6, 16.1)
Schwartz et al. (1996b) Cleveland (Cayahoga County), Ohio (88 - 90) PM_{10} mean = 43 µg/m^3 PM_{10} IQR = 26 – 56 µg/m^3	Review paper including an example drawn from respiratory hospital admissions of adults aged 65 yr and older (mean = 22/day) in Cleveland, OH. Categorical variables for weather and sinusoidal terms for filtering season employed.	Hospital admissions for respiratory illness of persons aged 65 yr and over in Cleveland strongly associated with PM_{10} and O_3, and marginally associated with SO_2 after control for season, weather, and day of the week effects.	<u>Respiratory HA's for persons 65+ years</u> 50 µg/m^3 PM_{10} ER = 5.8% (CI: 0.5, 11.4)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Zanobetti, et al. (2000a)+ Study Period: 86 - 94 Chicago (Cook Count), IL Population = 633,000 aged 65+ PM_{10} mean = 33.6 µg/m^3 PM_{10} range = 2.2, 157.3 µg/m^3	Analyzed HA's for older adults (65 + yr) for COPD (mean = 7.8/d), pneumonia (mean = 25.5/d), and CVD, using GLM Poisson regression controlling for temperature, dew point, barometric pressure, day of week, long wave cycles and autocorrelation, to evaluate whether previous admission or secondary diagnosis for associated conditions increased risk from air pollution. Effect modification by race, age, and sex also evaluated.	Air pollution- associated CVD HA's were nearly doubled for those with concurrent respiratory infections (RI) vs. those without concurrent RI. For COPD and pneumonia admissions, diagnosis of conduction disorders or dysrhythmias (Dyshr.) increased PM_{10} RR estimate. The PM_{10} RR effect size did not vary significantly by sex, age, or race, but baseline risks across these groups differ markedly, making such sub-population RR inter-comparisons difficult to interpret.	PM_{10} = 50 µg/m^3(average of lags 0,1) COPD (adults 65+ yrs.) W/o prior RI. ER = 8.8% (CI: 3.3, 14.6) With prior RI ER = 17.1% (CI: -6.7, 46.9) COPD (adults 65+ yrs.) W/o concurrent Dys. ER = 7.2% (CI: 1.3, 13.5) With concurrent Dys. ER = 16.5%(CI: 3.2, 31.5) Pneumonia (adults 65+ yrs.) W/o pr. Asthma ER = 11% (CI: 7.7, 14.3) With pr. Asthma ER = 22.8% (CI: 5.1, 43.6) Pneumonia (adults 65+ yrs.) W/o pr. Dyshr. ER = 10.4% (CI: 6.9, 14) With pr. Dyshr. ER = 18.8% (CI: 6.3, 32.7)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lippmann et al. (2000)* Detroit, MI ('92-'94) Population = 2.1 million PM_{10} Mean = 31 µg/m^3 (IQR= 19, 38 µg/m^3; max=105 µg/m^3) $PM_{2.5}$ Mean = 18 µg/m^3 (IQR= 10, 21 µg/m^3; max=86 µg/m^3) $PM_{10-2.5}$ Mean = 12 µg/m^3 (IQR= 8, 17 µg/m^3; max=50 µg/m^3) $SO_4^=$Mean = 5 µg/m^3 (IQR=1.8, 6.3 µg/m^3; max=34.5 µg/m^3) H^+ Mean = 8.8 nmol/m^3 = 0.4 µg/m^3 (IQR=0, 7nmol/m^3;max=279)	Respiratory (COPD and Pneumonia) HA's for persons 65 + yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity using LOESS smooths. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For respiratory HA's, all PM metrics yielded RR's estimates >1, and all were significantly associated in single pollutant models for pneumonia. For COPD, all PM metrics gave RR's >1, with H^+ being associated most significantly, even after the addition of O_3 to the regression. Adding gaseous pollutants had negligible effects on the various PM metric RR estimates. The most consistent effect of adding co-pollutants was to widen the confidence bands on the PM metric RR estimates: a common statistical artifact of correlated predictors. Despite usually non-detectable levels, H^+ had strong association with respiratory admissions on the few days it was present. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per µg/m^3 in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity is usually not present.	<u>Pneumonia HA's for 65+ yrs.</u> <u>No co-pollutant:</u> PM_{10} (50 µg/m^3) 1d lag ER = 22% (CI: 8.3, 36) $PM_{2.5}$ (25 µg/m^3) 1d lag: ER = 13% (CI: 3.7, 22) $PM_{2.5-10}$ (25 µg/m^3) 1d lag: ER = 12% (CI: 0.8, 24) H^+ (75 nmol/m^3) 3d lag: ER = 12% (CI: 0.8, 23) <u>O_3 co-pollutant (lag 3) also in model:</u> PM_{10} (50 µg/m^3) 1d lag, ER = 24% (CI: 8.2, 43) $PM_{2.5}$ (25 µg/m^3) 1d lag: ER = 12% (CI: 1.7, 23) $PM_{2.5-10}$ (25 µg/m^3) 1d lag: ER = 14% (CI: 0.0, 29) H^+ (75 nmol/m^3) 3d lag: ER = 11% (CI: -0.9, 24) <u>COPD Hospital Admissions for 65+ yrs.</u> <u>No co-pollutant:</u> PM_{10} (50 µg/m^3) 3d lag ER = 9.6% (CI: -5.1, 27) $PM_{2.5}$ (25 µg/m^3) 3d lag: ER = 5.5% (CI: -4.7, 17) $PM_{2.5-10}$ (25 µg/m^3) 3d lag: ER = 9.3% (CI: -4.4, 25) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: 0.0, 28) <u>O_3 co-pollutant (lag 3) also in model:</u> PM_{10} (50 µg/m^3) 3d lag, ER = 1.0% (-15, 20) $PM_{2.5}$ (25 µg/m^3) 3d lag: ER = 2.8% (CI: -9.2, 16) $PM_{2.5-10}$ (25 µg/m^3) 3d lag: ER = 0.3% (CI: -14, 18) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: -0.6, 28)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Ito (2003)	Re-analyses of Lippmann et al. (2000) with more stringent GAM convergence criteria and alternative models.	More stringent GAM generally, but not always, resuled in reduced RR estimates, but effect sizes not significantly different from originals. Extent fo reuction independent of risk estimate size. The reductions were not differential across PM components, so study conclusions unchanged.	**Pneumonia** (PM_{10}= 50 ug/m^3, LAG= 1D, No Co Poll): Default GAM: ER= 21.5 (8.3, 36) Strict GAM: ER=18.1 (5.3, 32.5) NS GLM: ER=18.6 (5.6, 33.1) **COPD** (PM_{10}= 50 ug/m^3, LAG= 3D, No Co Poll): Default GAM: ER= 9.6 (-5.3, 26.8) Strict GAM: ER=6.5 (-7.8, 23.0) NS GLM: ER=4.6 (-9.4, 20.8) **COPD** ($PM_{2.5}$,=25 ug/m^3, Lag=1D, No Co Poll): Default GAM: ER =5.5 (-4.7, 16.8) Strict GAM: ER=3.0(-6.9, 13.9) NS GLM: ER=0.3(-9.3, 10.9) **Pneumonia** ($PM_{2.5}$,=25 ug/m^3, LAG= 1D,No Co Poll): Default GAM: ER = 12.5 (3.7, 22.1) Strict GAM:ER = 10.5 (1.8, 19.8) NS GLM: 10.1 (1.5, 19.5)
Lumley and Heagerty (1999) Seattle (King Cty.), WA (87-94) Population = NR PM_1 daily mean = NR PM_{1-10} daily mean = NR From Sheppard et al, 1999: PM_{10} mean = 31.5 µg/m^3 PM_{10} IQR = 19-39 µg/m^3 $PM_{2.5}$ mean = 16.7 µg/m^3 $PM_{2.5}$ IQR = 8-21 µg/m^3	Estimating equations based on marginal generalized linear models (GLM) applied to respiratory HA's for persons <65 yrs. of age (mean ˜ 8/day) using class of variance estimators based upon weighted empirical variance of the estimating functions. Poisson regression used to fit a marginal model for the log of admissions with linear temperature, day of week, time trend, and dummy season variables. No co-pollutants considered.	PM_1 at lag 1 day associated with respiratory HA's in children and younger adults (<65), but not PM_{10-1}, suggesting a dominant role by the submicron particles in $PM_{2.5}$–asthma HA associations reported by Sheppard et al. (1999). 0-day lag PM_1 and 0 and 1 day lag PM_{1-10} had RR near 1 and clearly non-significant. Authors note that model residuals correlated at r=0.2, suggesting the need for further long-wave controls in the model (e.g., inclusion of the LOESS of HA's).	<u>Respiratory HA's for persons <65 yrs. old</u> PM_1 = 25 µg/m^3, no co-pollutant: 1-d lag ER = 5.9 (1.1, 11.0)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Moolgavkar et al. (2000)+ King County, WA (87 - 95) Population = NR PM_{10} mean = 30.0 µg/m^3 PM_{10} IQR =18.9-37.3 µg/m^3 $PM_{2.5}$ mean =18.1 µg/m^3 $PM_{2.5}$ IQR =10-23 µg/m^3	Association between air pollution and hospital admissions (HA's) for COPD (all age mean=7.75/day; 0-19 yrs. mean=2.33/day) investigated using Poisson GAM's controlling for day-of-week, season, and LOESS of temperature. Co-pollutants addressed: O_3, SO_2, CO, and pollens. $PM_{2.5}$ only had one monitoring site versus multiple sites averaged for other pollutants.	Of the PM metrics, PM_{10} showed the most consistent associations across lags (0-4 d). $PM_{2.5}$ yielded the strongest positive PM metric association at lag3 days, but gave a negative association at lag4 days. That $PM_{2.5}$ only had one monitoring site may have contributed to its effect estimate variability. Residual autocorrelations (not reported) may also be a factor. Adding gaseous co-pollutants or pollens decreased the $PM_{2.5}$ effect estimate less than PM_{10}. Analyses indicated that asthma HA's among the young were driving the overall COPD-air pollution associations.	<u>COPD HA's all ages</u> (no co-pollutant) PM_{10} (50 µg/m^3, lag 2) ER = 5.1% (CI: 0, 10.4) $PM_{2.5}$ (25 µg/m^3, lag 3) ER = 6.4% (CI: 0.9, 12.1) COPD HA's all ages (CO as co-pollutant) PM_{10} (50 µg/m^3, lag 2) ER = 2.5% (CI: -2.5, 7.8) $PM_{2.5}$ (25 µg/m^3, lag 3) ER = 5.6% (CI: 0.2, 11.3)
Moolgavkar (2000a)* Study Period: 1987-1995 <u>Chicago (Cook County), IL</u> Population = NR PM_{10} median = 35 µg/m^3 PM_{10} IQR = 25-47 µg/m^3 <u>Los Angeles (LA County), CA</u> Population = NR PM_{10} median = 44 µg/m^3 PM_{10} IQR = 33-59 µg/m^3 $PM_{2.5}$ median = 22 µg/m^3 $PM_{2.5}$ IQR = 15-31 µg/m^3 <u>Phoenix (Maricopa County), AZ</u> Population = NR PM_{10} median = 41 µg/m^3 PM_{10} IQR = 32-51 µg/m^3	Investigated associations between air pollution (PM_{10}, O_3, SO_2, NO_2, and CO) and COPD Hospital Admissions (HA's). $PM_{2.5}$ also analyzed in Los Angeles. HA's for adults >65 yr.: median=12/day in Chicago, =4/d in Phoenix; =20/d in LA. Analyses employed 30df to fit long wave. In LA, analyses also conducted for children 0-19 yr. (med.=17/d) and adults 20-64 (med.=24/d). Poisson GAM's used controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. PM data available only every 6th day (except for daily PM_{10} in Chicago), vs. every day for gases. Power likely differs across pollutants, but number of sites and monitoring days not presented. Two pollutant models forced to have same lag for both pollutants. Autocorrelations or intercorrelations of pollutant coefficients not presented or discussed.	For >64 adults, CO, NO_2 and O_3 (in summer) most consistently associated with the HA's. PM effects more variable, especially in Phoenix. Both positive and negative significant associations for PM and other pollutants at different lags suggest possible unaddressed negative autocorrelation. In LA, PM associated with admissions in single pollutant models, but not in two pollutant models. The forcing of simultaneous pollutants to have the same lag (rather than maximum lag), which likely maximizes intercorrelations between pollutant coefficients, may have biased the two pollutant coefficients, but information not presented. Analysis in 3 age groups in LA yielded similar results. Author concluded that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER Single Pollutant Models: <u>COPD HA's (>64 yrs.)</u> (50 µg/m^3 PM_{10}): Chicago: Lag 0 ER =2.4% (CI: -0.2, 4.3) LA: Lag 2 ER = 6.1% (CI: 1.1, 11.3) Phoenix: Lag 0 ER = 6.9% (CI: -4.1, 19.3) <u>LA COPD HA's</u> (50 µg/m^3 PM_{10}, 25 µg/m^3 $PM_{2.5}$ or $PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=10.7%(CI: 4.4, 17.3) (0-19 yrs.): $PM_{2.5}$ lg0=4.3%(CI: -0.1, 8.9) (0-19 yrs.): $PM_{(2.5-10)}$ lg2=17.1%(CI: 8.9, 25.8) (20-64 yrs.): PM_{10} lg2=6.5%(CI: 1.7, 11.5) (20-64 yrs.): $PM_{2.5}$ lg2=5.6%(CI: 1.9, 9.4) (20-64 yrs.): $PM_{2.5-10}$ lg2=9%(CI: 3, 15.3) (> 64 yrs): PM_{10} lg2 = 6.1% (1.1, 11.3) (> 64 yrs): $PM_{2.5}$ lg2 = 5.1% (0.9, 9.4) (>64 yrs.): $PM_{2.5-10}$ lg3=5.1% (CI: -0.4, 10.9) (>64 yr) 2 Poll. Models (CO = co-poll.) PM_{10}: Lag 2 ER = 0.6% (CI: -5.1, 6.7) $PM_{2.5}$: Lag 2 ER = 2.0% (-2.9, 7.1)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Moolgavkar (2003)	Re-analyses of Moolgavkar (2000a) with more stringent GAM convergence criteria and alternative models.	GAM effect estimates virtually unchanged from originals using when GAM stringent criteria applied in LA (direct comparisons not possible in Chicago). In LA, changes in spline degrees of freedom had much more influence on effect size than the change in convergence criteria, especially for PM_{10}. In Chicago, small insignificant association of PM_{10} in the original work actually increased and became significant with the 100df model. Authors conclude the "basic qualitative conclusions unchanged".	LA COPD (all ages), LAG= 2D, PM_{10} =50ug/m3 Default GAM:30df** ER= 7.36% (CI:4.32-11.39) Strict GAM:30df ER= 7.78% (CI:4.32-10.51) Strict GAM: 100df ER = 7.78% (CI:4.32-10.51) NS GLM: 100df ER=5.00% (CI:1.22, 8.91) LA COPD (all ages), LAG=2D, $PM_{2.5}$ =25 ug/m3 Default GAM:30df** ER=4.82% (CI:2.44, 7.25) Strict GAM:30df ER=4.69% (CI:2.06, 7.38) Strict GAM: 100df ER=2.87% (CI:0.53, 5.27) NS GLM: 100df ER=2.59% (CI:-0.29, 5.56) Chicago COPD (>64yrs) LAG= 0D, PM_{10}=50ug/m^3 Default GAM (30df) ER =2.4% (CI: --0.2, 4.3) Default GAM (100df) not provided for comparison Strict GAM (100df) ER=3.24% (CI:0.031-6.24)
Sheppard et al. (1999)* Seattle, WA, Pop. = NR 1987-1994 PM_{10} mean = 31.5 µg/m^3 PM_{10} IQR = 19-39 µg/m^3 $PM_{2.5}$ mean = 16.7 µg/m^3 $PM_{2.5}$ IQR = 8-21 µg/m^3 $PM_{2.5-10}$ mean = 16.2 µg/m^3 $PM_{2.5-10}$ IQR = 9-21 µg/m^3	Daily asthma hospital admissions (HA's) for residents aged <65 (mean=2.7/day) regressed on PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, SO_2, O_3, and CO in a Poisson regression model with control for time trends, seasonal variations, and temperature-related weather effects. Appendicitis HA's analyzed as a control. Except O_3 in winter, missing pollutant measures estimated in a multiple imputation model. Pollutants varied in number of sites available for analysis, CO the most (4) vs. 2 for PM.	Asthma HA's significantly associated with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ mass lagged 1 day, as well as CO. Authors found PM and CO to be jointly associated with asthma admissions. Highest increase in risk in spring and fall. Results conflict with hypothesis that wood smoke (highest in early study years and winter) would be most toxic. Associations of CO with respiratory HA's taken by authors to be an index of incomplete combustion, rather than direct CO biological effect.	<u>Asthma Admissions (ages 0-64)</u> PM_{10} (lag=1day); 50 µg/m^3 ER = 13.7% (CI: 5.5%, 22.6) $PM_{2.5}$ (lag=1day); 25 µg/m^3 ER = 8.7% (CI: 3.3%, 14.3) $PM_{2.5-10}$ (lag=1day); 25 µg/m^3 ER = 11.1% (CI: 2.8%, 20.1)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Sheppard (2003)	Re-analyses of Sheppard et al. (1999) with more stringent GAM convergence criteria and alternative models.	The author notes that "While the biases from computational details of the fitting were small, they are not completely trivial given the small effects of interest." She concludes that: "Overall the results did not change meaningfully".	Asthma (ages 0-64) LAG=1day, PM_{10}=50 ug/m^3 No Co-Poll: Default GAM: ER = 13.7% (CI: 5.5%, 22.6) Strict GAM: ER= 8.1 (0.1, 16.7) NS GLM : ER=10.9 (2.8, 19.6) Asthma (all ages) LAG=1day, $PM_{2.5}$=25 ug/m^3 No Co-Poll: Default GAM : ER= 8.7% (3.3, 14.3) Strict GAM: ER=6.5% (1.1,12.0) NS GLM: ER= 8.7% (3.3,14.4) With Co-poll: Strict GAM: ER=6.5 (2.1, 10.9) NS GLM: ER=6.5 (2.1, 10.9)
Freidman et al. (2001) Atlanta, GA Summer 1996/control vs. Olympics PM_{10} decrease for 36.7 µg/m^3 to 30.8 µg/m^3	Asthma events in children aged 1 to 16 years were related to pollutant levels contrasting those during the Summer Olympics games during a 17 day period to control periods before and after the Olympics. GEE Poisson regression with autoregressive terms employed.	Asthma events were reduced during the Olympic period. A significant reduction in asthma events was associated with ozone concentration. The high correlation between ozone and PM limit the ability to determine which pollutants may have accounted for the reduction in asthma events.	3 day cumulative exposure PM_{10} per 10 µg/m^3 1.0 (0.80-2.48)
Zanobetti and Schwartz (2001)+ Cook County, Illinois 1988-1994 PM_{10}: 33 µg/m^3 median	Respiratory admissions for lung disease in persons with or without diabetes as a co-morbidity related to PM_{10} measures. The generalized additive model used nonparametric LOESS functions to estimate the relation between the outcome and each predictor. The covariates examined were temperature, prior day's temperature, relative humidity, barometric pressure, and day of week.	Weak evidence that diabetes modified the risks of PM_{10} induced respiratory hospital admissions while diabetes modified the risk of PM_{10} induced COPD admissions in older people. Found a significant interaction with hospital admissions for heart disease and PM with more than twice the risk in diabetics as in persons without diabetes.	<u>COPD</u> PM_{10} 10 µg/m^3 with diabetes 2.29 (-0.76-5.44) without diabetes 1.50 (0.42-2.60)
Janssen et al. (2002)+ 14 U.S. cities 1985-1994 see Samet et al. (2000a,b)	Regression coefficients of the relation between PM_{10} and hospital admissions for respiratory disease from Samet et al. (2000a,b) and prevalence of air conditioning (AC).	Regression coefficients of the relation between ambient PM_{10} and hospital admissions for COPD decreased with increasing percentage of homes with central AC.	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997b) Toronto, Canada (1992-1994), Pop. = 4 mill. $PM_{2.5}$ mean = 16.8 µg/m^3 $PM_{2.5}$ IQR = 8-23 µg/m^3 $PM_{2.5-10}$ mean = 11.6 µg/m^3 $PM_{2.5-10}$ IQR = 7-14 µg/m^3 PM_{10} mean = 28.4 µg/m^3 PM_{10} IQR = 16-38 µg/m^3 CoH mean = 0.8 (per 10^3 lin. ft.) CoH IQR = 0.5-1.1(per 10^3 lin ft) SO_4 mean = 57.1 nmole/m^3 SO_4 IQR = 14-71 nmole/m^3 H^+ mean = 5 nmole/m^3 H^+ IQR = 0-6 nmole/m^3	Hospital admissions (HA's) for respiratory diseases (tracheobronchitis, chronic obstructive long disease, asthma, pneumonia) analyzed using Poisson regression (adjusting for long-term temporal trends, seasonal variations, effects of short-term epidemics, day-of-week, ambient temperature and dew point). Both linear prefiltering Poisson regression and LOESS GAM models applied. Daily particle measures: $PM_{2.5}$, coarse particulate mass($PM_{10-2.5}$), PM_{10}, SO_4, H^+, and gaseous pollutants (O_3, NO_2, SO_2, and CO) evaluated.	Positive air pollution-HA associations found, with ozone being pollutant least sensitive to adjustment for co-pollutants. However, even after the simultaneous inclusion of O_3 in the model, the association with the respiratory hospital admissions were still significant for PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, $CoH_,$, SO_4, and H^+.	<u>Respiratory HA's all ages</u>(no co-pollutant) PM_{10} (50 µg/m^3, 4d avg. lag 0) ER = 10.6% (CI: 4.5 - 17.1) $PM_{2.5}$ (25 µg/m^3, 4d avg. lag 1) ER = 8.5% (CI: 3.4, 13.8) $PM_{2.5-10}$ (25 µg/m^3, 5d avg. lag 0) ER = 12.5% (CI: 5.2, 20.0) <u>Respiratory HA's all ages</u>(O_3 co-pollutant) PM_{10} (50 µg/m^3, 4d avg. lag 0) ER = 9.6% (CI: 3.5, 15.9) $PM_{2.5}$ (25 µg/m^3, 4d avg., lag 1) ER = 6.2% (1.0, 11.8) $PM_{2.5-10}$ (25 µg/m^3, 5d avg. lag 0) ER = 10.8% (CI: 3.7, 18.1)
Burnett et al. (1999)+ Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} (µg/m^3): 18, 16, 10 CP_{est} (µg/m^3): 12, 10, 8 $PM_{10\ est}$ (µg/m^3): 30, 27, 15	Daily hospitalizations for asthma (493, mean 11/day), obstructive lung disease (490-492, 496, mean 5/day), respiratory infection (464, 466, 480-487, 494, mean 13/day) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were <u>estimated</u>, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models. Applied with non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in respiratory outcome. In multi-pollutant models, there were no significant PM associations with any respiratory outcome (results not shown). Use of estimated PM metrics limits the interpretation of pollutant-specific results reported. However, results suggest that a linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when a full range of gaseous pollutants are also modeled.	Percent excess risk (95% CI) per 50 µg/m^3 PM_{10}; 25 µg/m^3 $PM_{2.5}$ and $PM_{(10-2.5)}$: <u>Asthma</u> $PM_{2.5}$ (0-1-2 d): 6.4 (2.5, 10.6) PM_{10} (0-1 d): 8.9 (3.7, 14.4) $PM_{10-2.5}$ (2-3-4 d): 11.1 (5.8, 16.6) <u>COPD</u> $PM_{2.5}$: 4.8 (-0.2, 10.0) PM_{10}: 6.9 (1.3, 12.8) $PM_{10-2.5}$ (2-3-4 d): 12.8 (4.9, 21.3) <u>Resp. Infection:</u> $PM_{2.5}$: 10.8 (7.2, 14.5) PM_{10}: 14.2 (9.3, 19.3) $PM_{10-2.5}$ (0-1-2 d): 9.3 (4.6, 14.2)
Burnett et al. (1997c) 16 Canadian Cities('81-91) Population=12.6 MM CoH mean=0.64(per 10^3 lin. ft) CoH IQR=0.3-0.8(per 10^3 lin ft)	Air pollution data were compared to respiratory hospital admissions (mean=1.46/million people/day) for 16 cities across Canada. Used a random effects regression model, controlling for long-wave trends, day of week, weather, and city-specific effects using a linear prefiltered random effects relative risk regression model.	The 1 day lag of 0_3 was positively associated with respiratory admissions in the April to December period, but not in the winter months. Daily maximum 1-hr. CoH from 11 cities and CO also positively associated with HA's, even after controlling for O_3.	<u>Respiratory HA's all ages (with O_3,CO)</u> CoH IQR = 0.5, lag 0: CoH ER = 3.1% (CI: 1.0-4.6%)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (2001b)+ Toronto, Canada 1980-1994 $PM_{2.5}$: 18 µg/m^3 $PM_{10-2.5}$: 16.2 µg/m^3 (both estimated values)	Respiratory admissions in children aged <2 years relates to mean pollution levels. O_3, NO_2, SO_2, and CO (ICD-9: 493 asthma; 466 acute bronchitis; 464.4 croup or pneumonia, 480-486). Time-series analysis adjusted with LOESS.	Summertime urban air pollution, especially ozone, increases the risk that children less than 2 years of age will be hospitalized for respiratory disease.	$PM_{2.5}$ lag 0 15.8% (t=3.29) $PM_{2.5}$ lag 0 with O_3 1.4% (0.24) $PM_{10-2.5}$ lag 1 18.3% (t=3.29) with O_3 4.5% (0.72)
Europe			
Atkinson et al. (1999a) London (92 - 94) Population = 7.2 MM PM_{10} Mean = 28.5 10^{th}-90^{th} IQR = 15.8-46.5 µg/m^3 BS mean = 12.7 µg/m^3 10^{th}-90^{th} IQR = 5.5-21.6 µg/m^3	All-age respiratory (mean=150.6/day), all-age asthma (38.7/day), COPD plus asthma in adults >64 yr. (22.9/day), and lower respiratory (64.1/day) in adults >64 yr (16.7/day) hospital admissions in London hospitals considered. Counts for ages 0-14, 15-64, and >64 yr also examined. Poisson GLM regression used, controlling for season, day-of-week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	Positive associations found between respiratory-related emergency hospital admissions and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} included simultaneously, size and significance of each was reduced. Authors concluded that SO_2 and PM_{10} are both indicators of the same pollutant mix in this city. SO_2 and PM_{10} analyses by temperature tertile suggest that warm season effects dominate. Overall, results consistent with earlier analyses for London, and comparable with those for North America and Europe.	PM_{10} (50 µg/m^3), no co-pollutant. All Respiratory Admissions: All age (lag 1d) ER = 4.9% (CI: 1.8, 8.1) 0-14 y (lag 1d) ER = 8.1% (CI: 3.5, 12.9) 15-64y (lag 2d) ER = 6.9% (CI: 2.1, 12.9) 65+ y (lag 3d) ER = 4.9% (CI: 0.8, 9.3) Asthma Admissions: All age (lag 3d) ER = 3.4% (CI: -1.8, 8.9) 0-14 y (lag 3d) ER = 5.4% (CI: -1.2, 12.5) 15-64 y(lag 3d) ER = 9.4% (CI: 1.1, 18.5) 65+ y.(lag 0d) ER = 12% (CI: -1.8, 27.7) COPD & Asthma Admissions (65+yrs.) (lag 3d) ER = 8.6% (CI: 2.6, 15) Lower Respiratory Admissions (65+ yrs.) (lag 3d) ER = 7.6% (CI: 0.9, 14.8)
Wordley et al. (1997) Study Period: 4/92 –3/94 Birmingham, UK Population = NR PM_{10} daily values: Mean = 25.6 µg/m^3 range = 2.8, 130.9 µg/m^3 PM_{10} 3 day running. mean: Mean = 25.5 µg/m^3 range = 7.3, 104.7 µg/m^3	Relation between PM_{10} and total HA's for respiratory (mean = 21.8/d), asthma (mn.=6.2/d), bronchitis (mn.=2.4/d), pneumonia (mn.=3.4/d), and COPD (mn.=3.2/d) analyzed, using log-linear regression after adjusting for day of week, month, linear trend, RH, and T (but not T-RH interaction). RR's compared for various thresholds vs. mean risk of HA.	PM_{10} positively associated with all HA's for respiratory, asthma, bronchitis, pneumonia, and COPD. Pneumonia, all respiratory, and asthma HA's also significantly positively associated with the mean of PM_{10} over the past three days, which gave 10 to 20% greater RR's per 10 µg/m^3, as expected given smaller day to day deviations. Other air pollutants examined but not presented, as "these did not have a significant association with health outcomes independent from that of PM_{10}".	50 µg/m^3 in PM_{10} All Respiratory HA's (all ages) (lag0d) ER = 12.6% (CI: 5.7, 20) Asthma HA's (all ages) (lag2d) ER = 17.6% (CI: 3, 34.4) Bronchitis HA's (all ages) (lag0d) ER= 32.6% (CI: 4.4, 68.3) Pneumonia HA's (all ages) (lag3d) ER = 31.9% (CI: 15, 51.4) COPD HA's (all ages) (lag1d) ER = 11.5% (CI: -3, 28.2)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh (10/92-6/95) Population = 0.45 MM PM_{10} mean. =20.7 µg/m^3 PM_{10} min/max=5/72 µg/m^3 PM_{10} 90th% - 10th% = 20 µg/m^3	Poisson log-linear regression models used to investigate relation of daily HA's with NO_2, O_3, CO, and PM_{10}. Adjustments made for seasonal and weekday variation, daily T (using 8 dummy variables), and wind speed. Separate analyses for age<65 yr. (mean resp HA = 3.4/day) and age >64 yr. (mean resp HA = 8.7/day), and for subjects with multiple HA's.	The two strongest findings were for cardiovascular HA's of people aged >64, which showed a positive association with PM_{10} as a mean of the 3 previous days. PM_{10} was consistently positively associated with Respiratory HA's in both age groups, with the greatest effect size in those >64, especially among those with >4 HA's during '81-'95. Weak significances likely contributed to by low population size.	Single Pollutant Models PM_{10} = 50 µg/m^3, mean of lags 1-3 Respiratory HA's (age<65) ER = 1.25 (-12.8, 17.5) Respiratory HA's (age>64) ER = 5.33 (-9.3, 22.3) Respiratory HA's (age>64, >4 HA's) ER = 7.93 (-19.0, 43.7)
McGregor et al. (1999) Birmingham, UK. Population = NR Mean PM_{10} = 30.0 µg/m^3	A synoptic climatological approach used to investigate linkages between air mass types (weather situations), PM_{10}, and all respiratory hospital admissions (mean= 19.2/day) for the Birmingham area.	Study results show distinct differential responses of respiratory admission rates to the six winter air mass types. Two of three types of air masses associated with above- average admission rates also favor high PM_{10} levels. This is suggestive of possible linkage between weather, air quality, and health.	NR
Hagen et al. (2000)+ Drammen, Sweden(11/94-12/97) Population = 110,000 PM_{10} mean = 16.8 µg/m^3 PM_{10} IQR = 9.8-20.9 µg/m^3	Examined PM_{10}, SO_2, NO_2, VOC's, and O_3 associations with respiratory hospital admissions from one hospital (mean = 2.2/day). Used Poisson GAM controlling for temperature and RH (but not their interaction), long-wave and seasonality, day-of-week, holidays, and influenza epidemics.	As a single pollutant, the PM_{10} effect was of same order of magnitude as reported in other studies. The PM_{10} association decreased when other pollutants were added to the model. However, the VOC's showed the strongest associations.	Respiratory Hospital Admissions(all ages) For IQR=50 µg/m^3 -Single Pollutant Model: PM_{10} (lag 0) ER = 18.3% (CI: -4.2, 46) -Two Pollutant Model (with O_3): PM_{10} (lag 0) ER = 18.3% (CI: -4.2, 45.4) -Two Pollutant Model (with Benzene): PM_{10} (lag 0) ER = 6.5% (CI:-14 , 31.8)
Dab et al. (1996) Paris, France (87 - 92) Population = 6.1 MM PM_{13} mean = 50.8 µg/m^3 PM_{13} 5th-95th range = 19.0-137.3 BS mean = 31.9 µg/m^3 BS 5th-95th Range =11.0-123.3	Daily mortality and general admissions to Paris public hospitals for respiratory causes were considered (means/day: all resp.=79/d, asthma=14/d, COPD=12/d). Time series analysis used linear regression model followed by a Poisson regression. Epidemics of influenza A and B, temperature, RH, holidays, day of week, trend, long-wave variability, and nurses' strike variables included. No two pollutant models considered.	For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association across outcomes. Asthma was significantly correlated with NO_2 levels, but not PM_{13}.	For PM_{13} = 50 µg/m^3 ; BS = 25 µg/m^3; 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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (1997) Amsterdam(77 - 89) Barcelona (86- 92) London (87 - 91) Milan (80- 89) Paris (87 - 92) Rotterdam (77 - 89) Populations .= 0.7(A), 1.7(B), 7.2(L),1.5(M),6.5(P),0.6(R)MM BS Means = 6, 41, 13, -, 26, 22 TSP Means = 41,155, -, 105, -,41	All-age daily hospital admissions (HA's) for COPD considered in 6 APHEA cities; Mean/day = 1.1(A), 11(B), 20(L), 5(M), 11(P), 1.1(R). Poisson GLM regression controlling for day of week, holidays, seasonal and other cycles, influenza epidemics, temperature, RH, and autocorrelation. Overall multi-city estimates made using inverse variance wts., allowing for inter-city variance.	Ozone gave the most consistent associations across models. Multi-city meta-estimates also indicated associations for BS and TSP. The warm/cold season RR differences were important only for ozone, having a much stronger effect in the warm season. COPD effect sizes found were much smaller than in U.S. studies, possibly due to inclusion of non-emergency admissions or use of less health-relevant PM indices.	BS (25 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 1.7% (0.5, 2.97) TSP (100 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 4.45% (CI: -0.53, 9.67)
Díaz et al. (1999) Madrid (94 - 96) Population = NR TSP mean 40 $\mu g/m^3$	ARIMA modeling used to analyze emergency respiratory and circulatory admissions (means/day=7.8,7.6) from one teaching hospital. Annual, weekly, and 3 day periodicities controlled, but no time trend included, and temperature crudely fit with v-shaped linear relationship.	Although TSP correlated at zero lag with admissions in winter and year-round, TSP was never significant in ARIMA models; so effect estimates not reported for TSP. Also, found biologically implausible u-shaped relationship for O_3, possibly indicating unaddressed temperature effects.	N/A
Spix et al. (1998) London (L) (87 - 91) Pop. =7.2 Million (MM) BS Mean = 13 $\mu g/m^3$ Amsterdam (A) (77 - 89) Pop. =0.7 MM BS Mean = 6 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Rotterdam (R) (77 - 89) Pop. =0.6MM BS Mean = 22 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Paris (P) (87 - 92), Pop.= 6.14 MM BS Mean = 26 $\mu g/m^3$ Milano (M) (80 - 89) Pop. = 1.5 MM TSP Mean =120 ($\mu g/m^3$)	Respiratory (ICD9 460-519) HA's in age groups 15-64 yr and 65 + yrs. related to SO_2, PM (BS or TSP), O_3, and NO_2 in the APHEA study cities using standardized Poisson GLM models with confounder controls for day of week, holidays, seasonal and other cycles, temperature, RH, and autocorrelation. PM lag considered ranged from 0-3 day, but varied from city to city. Quantitative pooling conducted by calculating the weighted means of local regression coefficients using a fixed-effects model when no heterogeneity could be detected; otherwise, a random-effects model employed.	Pollutant associations noted to be stronger in areas where more than one monitoring station was used for assessment of daily exposure. The most consistent finding was an increase of daily HA's for respiratory diseases (adults and elderly) with O_3. The SO_2 daily mean was available in all cities, but SO_2 was not associated consistently with adverse effects. Some significant PM associations were seen, although no conclusion related to an overall particle effect could be drawn. The effect of BS was significantly stronger with high NO_2 levels on the same day, but NO_2 itself was not associated with HA's. Authors concluded that "there was a tendency toward an association of respiratory admissions with BS, but the very limited number of cities prevented final conclusions."	Respiratory Admissions (BS = 25 $\mu g/m^3$) BS (L, A, R, P) 15-64 yrs: 1.4% (0.3, 2.5) 65+ yrs: 1.0% (-0.2, 2.2) TSP (A, R, M) (100 $\mu g/m^3$) 15-64 yrs: 2.0 (-2.1, 6.3) 65+ yrs: 3.2 (-1.2, 7.9) Respiratory HA's BS (L, A, R, P): Warm (25 $\mu g/m^3$) 15-64 yrs: -0.5% (-5.2, 4.4) 65+ yrs: 3.4% (-0.1, 7.1) BS (L, A, R, P): Cold (25 $\mu g/m^3$) 15-64 yrs: 2,0% (0.8, 3.2) 65+ yrs: 0% (-2.2, 2.3) TSP (A, R, M): Warm (100 $\mu g/m^3$) 15-64 yrs: 6.1% (0.1, 12.5) 65+ yrs: 2.0% (-3.9, 8.3) TSP (A, R, M): Cold (100 $\mu g/m^3$) 15-64 yrs: -5.9% (-14.2, 3.2) 65+ yrs: 4.0% (-0.9, 9.2)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Vigotti et al. (1996) Study Period.: 80 - 89 Milan, IT Population = 1.5 MM TSP mean = 139.0 µg/m^3 TSP IQR = 82.0, 175.7 µg/m^3	Association between adult respiratory HA's (15-64 yr mean =11.3/day, and 65 + yr mean =8.8/day) and air pollution evaluated, using the APHEA protocol. Poisson regression used with control for weather and long term trend, year, influenza epidemics, and season	Increased risk of respiratory HA was associated with both SO_2 and TSP. The relative risks were similar for both pollutants. There was no modification of the TSP effect by SO_2 level. There was a suggestion of a higher TSP effect on hospital admissions in the cool months.	Young Adult (15-64 yrs.) Resp. HA's 100 µg/m^3 increase in TSP Lag 2 ER = 5% (CI: 0, 10) Older Adult (65+ yrs.) Resp. HA's 100 µg/m^3 increase in TSP Lag 1 ER = 5% (CI: -1, 10)
Anderson et al. (1998) London (87 - 92) Population = 7.2 MM BS daily mean = 14.6 µg/m^3 BS 25-75th IQR = 24-38	Poisson GLM log-linear regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 yr. (mean=19.5/d), 15-64 yr. (mean=13.1/d) and 65 + yr. (mean =2.6/d). Analysis controlled for time trends, seasonal factors, calendar effects, influenza epidemics, RH, temperature, and auto-correlation. Interactions with co-pollutants and aeroallergens tested via 2 pollutant models and models with pollen counts (grass, oak and birch).	Daily hospital admissions for asthma found to have associations with O_3, SO_2, NO_2, and particles (BS), but there was lack of consistency across the age groups in the specific pollutant. BS association was strongest in the 65 + group, especially in winter. Pollens not consistently associated with asthma HA's, sometimes being positive, sometimes negative. Air pollution associations with HA's not explained by airborne pollens in simultaneous regressions, and there was no consistent pollen-pollutant interaction.	Asthma Admissions. BS=25 µg/m^3 BS Lag = 0-3 day average concentration All age ER = 5.98% (0.4, 11.9) <15yr. ER = 2.2% (-4.6, 9.5) 15-64yr ER = 1.2% (-5.3, 8.1) 65+ yr. ER = 22.8% (6.1, 42.5) BS=50 µg/m^3, 2d lag & co-pollutant: Older Adult (>64 yrs.) Asthma Visits: BS alone: ER = 14.6% (2.7, 27.8) &O_3: ER = 20.0% (3.0, 39.8) & NO_2: ER = 7.4% (-8.7, 26.5) SO_2: ER = 11.8% (-2.2, 27.8)
Kontos et al. (1999) Piraeus, Athens GR (87 - 92) Population = NR BS mean =46.5 µg/m^3 BS max =200 µg/m^3	Relation of respiratory HA's for children (0-14 yrs.) (mean = 4.3/day) to BS, SO_2, NO_2, and O_3 evaluated, using a nonparametric stochastic dynamical system approach and frequency domain analyses. Long wave and effects of weather considered, but non-linearity and interactions of T and RH relation with HA's not addressed.	Pollution found to explain significant portion of the HA variance. Of pollutants considered, BS was consistently among most strongly explanatory pollutants across various reported analyses.	NR

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Ponce de Leon et al. (1996) London (4/87-2/92) Population = 7.3 million BS mean. =14.6 μg/m^3 BS 5th-95th %=6 - 27 μg/m^3	Poisson GLM log-linear regression analysis of daily counts of HA's (means/day: all ages=125.7; Ages 0-14=45.4; Ages 15-64=33.6; Ages 65+=46.7). Effects of trend, season and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity, and autocorrelation addressed. However, temperature modeled as linear, with no RH interaction. Pollution variables were BS, SO_2, O_3, and NO_2, lagged 0-3 days.	O_3 associated with increase in daily HA's, especially in the "warm" season. However, u-shape of the O_3 dose-response suggests that linear temperature control was not adequate. Few significant associations with other pollutants, but these tended to be positive (especially in cold season, Oct-March, and for older individuals for BS).	<u>Respiratory HA's (all ages)</u> Single Pollutant Models For Oct-Mar. BS = 25 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) <u>Respiratory HA's (>65)</u> 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)
Schouten et al. (1996) Amsterdam/Rotterdam (77 - 89) Amsterdam Pop. = 0.69 Million Rotterdam Pop. = 0.58 Million Amsterdam, NE BS mean. =11 μg/m^3 BS 5th-95th% = 1 - 37 μg/m^3 Rotterdam, NE BS mean. =26 μg/m^3 BS 5th-95th %= 6 -61 μg/m^3	Daily emergency HA's for respiratory diseases (ICD 460-519), COPD (490-492, 494, 496), and asthma (493). The mean HA/d (range) for these were: 6.70 (0-23), 1.74 (0-9) and 1.13 (0-7) respectively in Amsterdam and 4.79 (0-19), 1.57 (0-9), and 0.53 (0-5) in Rotterdam. HA associations with BS, O_3, NO_2, and SO_2 analyzed, using autoregressive Poisson GLM regression allowing for overdispersion and controlling for season, day of week, meteorological factors, and influenza epidemics.	BS did not show any consistent effects in Amsterdam; but in Rotterdam BS was positively related to HA's. Most consistent BS associations in adults >64 yrs. in winter. Positive O_3 association in summer in people aged >64 in Amsterdam and Rotterdam. SO_2 and NO_2 did not show any clear effects. Results not changed in pollutant interaction analyses. The authors concluded short-term air pollution-emergency HA's association is not always consistent at these individual cities' relatively low counts of daily HA's and low levels of air pollution. Analyses for all ages of all the Netherlands gave a strong BS-HA association in winter.	Single Pollutant Models For BS=25 μg/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)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Sunyer et al. (1997) Barcelona (86 - 92) Population = NR BS Median: 40 µg/m^3 BS Range: 11-258 (B Helsinki (86 - 92) Population = NR BS Median: - BS Range: - Paris (86 - 92) Population = NR BS Median: 28 µg/m^3 BS Range: 4-186 µg/m^3 London (86 - 92) Population = NR BS Median: 13 µg/m^3 BS Range: 3-95 µg/m^3	Evaluated relations of BS, SO_2, NO_2, and O_3 to daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)]. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities: ED visits in Barcelona; emergency hospital asthma admissions in London and Helsinki, and total asthma admissions in Paris. Estimates from all cities obtained for entire period and also by warm or cold seasons, using Time-series GLM regression, controlling for temperature and RH, viral epidemics, day of week effects, and seasonal and secular trends applied using the APHEA study approach. Combined associations were estimated using meta-analysis.	Daily admissions for asthma in adults increased significantly with increasing ambient levels of NO_2, and positively (but non-significantly) with BS. The association between asthma admissions and pollution varied across cities, likely due to differing asthma outcomes considered. In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with BS and NO_2, though the latter only in cold seasons. No association observed in children for O_3. Authors concluded that "In addition to particles, NO_2 and SO_2 (by themselves or as a constituent of a pollution mixture) may be important in asthma exacerbations".	ER per 25 µg/m^3 BS (24 h Average) Asthma Admissions/Visits: <15 yrs.: London ER = 1.5% (lg 0d) Paris ER = 1.5% (lg 2d) Total ER = 1.5% (-1.1, 4.1) 15-64 yrs: Barcelona ER = 1.8% (lg 3d) London ER = 1.7% (lg 0d) Paris ER = 0.6% (lg 0d) Total ER = 1.0% (-0.8, 2.9) Two Pollutant (per 25 µg/m^3 BS) Asthma Admissions (24 h Avg) <15 yrs, (BS & NO_2): London ER = 0.6% (lg 0d) Paris ER = 2.9% (lg 2d) Total ER = 1.8% (-0.6, 4.3) <15 yrs, (BS & SO_2): London ER = -1.1% (lg 0d) Paris ER = -1.4% (lg 2d) Total ER = -1.3 (-5.0, 2.5) 15-64 yrs, (BS & NO_2): Barcelona ER = 1.5% (lg 0d) London ER = -4.7% (lg 0d) Paris ER = -0.7% (lg 1d) Total ER = -0.5% (-5.1, 4.4)
Tenías et al (1998) Study Period.: 94 - 95 Valencia, Spain Hosp. Cachment Pop. =200,000 BS mean = 57.7 µg/m^3 BS IQR = 25.6-47.7 µg/m^3	Associations between adult (14+ yrs.) emergency asthma ED visits to one city hospital (mean =1.0/day) and BS, NO_2, O_3, SO_2 analyzed, using GLM Poisson auto-regressive modeling, controlling for potential confounding weather and time (e.g., seasonal) and trends using the APHEA protocol.	Association with asthma was positive and more consistent for NO_2 and O_3 than for BS or SO_2. Suggests that secondary oxidative-environment pollutants may be more asthma relevant than primary reduction-environment pollutants (e.g., carbonaceous particles). NO_2 had greatest effect on BS in co-pollutant models, but BS became significant once 1993 was added, showing power to be a limitation of this study.	Adult Asthma HA's, BS = 25 µg/m^3 For 1993-1995: Lag 0 ER = 10.6% (0.9, 21.1) For 1994-1995: Lag 0 ER = 6.4% (-4.8, 18.8)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (2001) West Midland, England (October 1994-December 1996) Population = 2.3 million PM_{10} mean = 23.3 µg/m^3 $PM_{2.5}$ mean = 14.5 µg/m^3 $PM_{10-2.5}$ = 9.0 µg/m^3 (by subtraction)	Respiratory hospital admissions (mean = 66/day) related to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, SO_4^-, NO_2, O_3, SO_2, CO. GLM regression with quasi-likelihood approach, controlling for seasonal patterns, temp, humidity, influenza episodes, day week. Adjusted for residual serial correlation and over-dispersion.	Respiratory admissions (all ages) not associated with any pollutant. Analyses by age revealed some associations to PM_{10} and $PM_{2.5}$ and respiratory admissions in the 0-14 age group. There was a striking seasonal interaction in the cool season versus the warm season. $PM_{10-2.5}$ effects cannot be excluded. Two pollutant models examined particulate measures. $PM_{2.5}$ effects reduced by inclusion of black smoke.	Respiratory HA - lag 0+1 days PM_{10} Increment10-90% (11.4-38.3 µg/m^3) All ages: 1.5 (-0.7 to 3.6) Ages 0-14: 3.9 (0.6 to 7.4) Ages 15-64: 0.1 (-4.0 to 4.4) Ages 65: -1.1 (-4.3 to 2.1) $PM_{2.5}$ (6.0-25.8) All ages: 1.2 (-0.9 to 3.4) Ages 0-14: 3.4 (-0.1 to 7.0) Ages 15-64: -2.1 (-6.4 to 2.4) Ages 65: -1.3 (-4.7 to 2.2) $PM_{10-2.5}$ (4.1 to 15.2) All ages: 0.2 (-2.5 to 3.0) Ages 0-14: 4.4 (-0.3 to 9.4) Ages 15-64: -4.9 (-9.9 to 0.4) Ages 65: -1.9 (-6.0 to 2.5) COPD (ICD-9 490-492, 494-496) PM_{10} Age 65: -1.8 (-6.9 to 3.5) $PM_{2.5}$ Age 65: -3.9 (-9.0 to 1.6) $PM_{10-2.5}$ Age 65: -1.7 (-8.9 to 5.3) Asthma (ICD- 9-493) (mean lag 0+1) PM_{10} Ages 0-14: 8.3 (1.7 to 15.3) Ages 15-64: -2.3 (-10.0 to 6.1) $PM_{2.5}$ Ages 0-14: 6.0 (-0.9 to 13.4) Ages 15-64: -8.4 (-16.4 to 0.3) $PM_{10-2.5}$ Ages 0-14: 7.1 (-2.1 to 17.2) Ages 15-64: -10.7 (-19.9 to -0.5)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Atkinson et al. (2001)+ Eight city study: Median/range Barcelona 1/94 - 12/96 PM_{10} 53.3 µg/m^3 (17.1, 131.7) Birmingham 3/92 -12/94 PM_{10} 21.5 µg/m^3 (6.5, 115) London 1/92 - 12/94 PM_{10} 24.9 µg/m^3 (7.2, 80.4) Milan -No PM_{10} Netherlands 1/92 - 9/95 PM_{10} 33.4 µg/m^3 (11.3, 130.8) Paris 1/92 - 9/96 PM_{10} 20.1 µg/m^3 (5.8, 80.9) Rome - No PM_{10} Stockholm 3/94 - 12/96 PM_{10} 13.6 µg/m^3 (4.3, 43.3)	As part of the APHEA 2 project, association between PM_{10} and daily counts of emergency hospital admissions for Asthma (0-14 and 15-64 yrs), COPD and all-respiratory disease (65+ yrs) regressed using GAM, controlling for environmental factors and temporal patterns.	This study reports that PM was associated with daily admissions for respiratory disease in a selection of European cities. Average daily ozone levels explained a large proportion of the between-city variability in the size of the particle effect estimates in the over 65 yr age group. In children, the particle effects were confounded with NO_2 on a day-to-day basis.	For 10 µg/m^3 increase **Asthma Admission Age 0-14 yrs**: PM_{10} for cities ranged from -0.9% (-2.1, 0.4) to 2.8% (0.8, 4.8) with an overall effect estimate of 1.2% (0.2, 2.3) **Asthma Admission Age 15-64 yrs:** Overall PM 1.1% (0.3, 1.8) **Admission of COPD and Asthma Age 65+ years:** Overall PM 1.0% (0.4, 1.5) **Admission All Respiratory Disease Age 65+ years:** Overall PM 0.9% (0.6, 1.3)
Thompson et al. (2001) Belfast, Northern Ireland 1/1/93 – 12/31/95. PM_{10} µg/m^3 mean (SD) May – October 24.9 (13.7) November – April 31.9 (24.3)	The rates of acute asthma admission to children's emergency was studied in relation to day-to-day fluctuation of PM_{10} and other pollutants using GLM Poisson regression.	A weak, but significant association between PM10 concentration and asthma emergency-department admissions was seen. After adjusting for multiple pollutants only the benzene level was independently associated with asthma emergency department admission. Benzene was highly correlated to PM_{10}, SO_2 and NO_2 levels.	—
Fusco et al. (2001)+ Rome, Italy 1995-1997 PM – suspended particles measured	Daily counts of hospital admissions for total respiratory conditions, acute respiratory infection including pneumonia, COPD, and asthma was analyzed in relation to PM measures and gaseous pollutants using generalized additive GAM models controlling for mean temperature, influenza, epidermics, and other factors using spline smooths.	No effect was found for PM. Total respiratory admission were significantly associated with same-day level of NO_2 and CO. There was no indication that the effects of air pollution were present at lags >2 days. Among children, total respiratory and asthma admissions were strongly associated with NO_2 and CO. Multipollutant model analysis yielded weaker and more unstable results.	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America			
Braga et al. (1999) São Paulo, Brazil (92 - 93) Population = NR PM_{10} mean = 66.3 µg/m^3 PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) to public hospitals serving 40% of the population were regressed (using both GLM and GAM) on air pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Air pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". Associations ascribed primarily to auto emissions by the authors.	PM_{10} (50 µg/m^3), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) GLM Model: (0-5day lg avg.) ER = 8.9% (CI: 4.6, 13.4) GAM Model (0-5day lg avg.) ER = 8.3% (CI: 4.1, 12.7)
Gouveia and Fletcher (2000) Study Period. 92-94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 µg/m^3 PM_{10} IQR = 42.9-75.5 µg/m^3 PM_{10}10/90th% =98.1 µg/m^3 PM_{10} 95th% = 131.6 µg/m^3	Daily public hospital respiratory disease admissions for children (mean resp. < 5y = 56.1/d; mean pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean pneum.<1y=24.0) and daily levels air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) and were analyzed with Poisson regression. GLM Models adjusted for time trends, seasonal patterns, weekdays, holidays, weather, and serial correlation. PM_{10} measured by Beta-gauge. Private hospitals serving wealthier citizens not in database.	Children's HA's for total respiratory and pneumonia positively associated with O_3, NO_2, and PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with other reports, but smaller RR's. This may be due to higher baseline admission rates in this poor sub-population vs. other studies, but this was not intercompared by the authors.	PM_{10} = 50 µg/m^3: All Respiratory HA's for children < 5yrs. ER = 2.0% (-0.8, 4.9) Pneumonia HA's for children <5 yrs. ER = 2.5% (-0.8, 6.0) Asthma HA's for children <5 yrs. ER = 2.6% (-4.0, 9.7) Pneumonia HA's for children <1 yrs. ER = 4.7% (0.7, 8.8)
Rosas et al. (1998) SW Mexico City (1991) Population = NR PM_{10} mean. =77 µg/m^3 PM_{10} min/max= 25/183 µg/m^3	Log-regression GLM analysis of relations between emergency hospital admissions for asthma for children <15 yrs (mean=2.5/day), adults (mean=3.0/day), and adults >59 yrs (mean=0.65/day) and lag 0-2 d pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	Few statistical associations were found between asthma admissions and air pollutants. Grass pollen was associated with child and adult admissions, and fungal spores with child admissions. Authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Australia			
Morgan et al. (1998) Sydney, AU (90 - 94) Population = NR $PM_{2.5}$ 24 h mean = 9.6 µg/m^3 $PM_{2.5}$ 10th-90th% = 3.6-18 µg/m^3 $PM_{2.5}$ max-1 h mean = 22.8 µg/m^3 $PM_{2.5}$ 10th-90th% = 7.5-44.4 µg/m^3	A Poisson analysis, controlled for overdispersion and autocorrelation via generalized estimating equations (GEE), of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day), COPD (mean 65+yrs =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM. The authors cited the error introduced by estimating $PM_{2.5}$ and the low PM levels as possible reasons for the weak PM-respiratory HA associations.	Asthma HA's Single Pollutant Model: For 24 hr $PM_{2.5}$ = 25 µg/m^3 1-14 yrs.(lag1) ER = -1.5% (CI: -7.8, 5.3) 15-64 yrs.(lag0) ER = 2.3% (CI: -4, 9) For 1h $PM_{2.5}$ =25 µg/m^3 1-14 yrs.(lag1) ER = + 0.5% (CI: -1.9, 3.0) 15-64 yrs.(lag0) ER = 1.5% (CI: -0.9, 4) Multiple Pollutant Model: For 24h $PM_{2.5}$ = 25 µg/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 µg/m^3 (lag 0) ER =4.2% (CI: -1.5, 10.3) For 1h $PM_{2.5}$ = 25 µg/m^3 (lag 0) ER = 2% (CI: -0.3, 4.4) Multiple Pollutant Model: For 1h $PM_{2.5}$ = 25 µg/m^3 (lag 0) ER = 1.5% (CI: -0.9, 4)
Asia			
Tanaka et al. (1998) Stdy Pd.:1/92-12/93 Kushiro, Japan Pop. = 102 adult asthmatics PM_{10} mean = 24.0 µg/m^3 PM_{10} IQR = NR	Associations of HA's for asthma (in 44 non-atopic and 58 atopic patients) with weather or air pollutants (NO, NO_2, SO_2,PM_{10}, O_3, and acid fog) evaluated. Odds ratios (OR) and 95% CI's calculated between high and low days for each environmental variable. Poisson GLM regression was performed for the same dichototomized variables.	Only the presence of acid fog had a significant OR >1.0 for both atopics and non-atopics. PM_{10} associated with a reduction in risk (OR<1.0) for both atopics and non-atopics. Poisson regression gave a non-significant effect by PM_{10} on asthma HA's. However, no long-wave or serial auto-correlation controls applied, so the opposing seasonalities of PM vs. HA's indicated in time series data plots are likely confounding these results.	For same-day (lag=0) PM_{10} Adult Asthma HA's OR for <30 vs. >30 µg/m^3 PM_{10}: Non-atopic OR = 0.77 (CI: 0.61, 0.98) Atopic OR = 0.87 (CI: 0.75, 1.02) Poisson Coefficient for PM_{10} > 30 µg/m^3 Non-atopic = -0.01 (SE = 0.15) Atopic = -0.002 (SE = 0.09)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Asia (cont'd)			
Wong et al. (1999a) Study Period.: 94 - 95 Hong Kong Population = NR PM_{10} mean = 50.1 µg/m^3 PM_{10} median = 45.0 µg/m^3 PM_{10} IQR = 30.7, 65.5 µg/m^3	Poisson GLM regression analyses were applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated. Using the APHEA protocol, models accounted for time trend, season and other cyclical factors, T, RH, autocorrelation and overdispersion. PM_{10} measured by TEOM, which likely underestimates mass.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}. No significant respiratory HA interactions with PM_{10} effect were found for high NO_2, high O_3, or cold season.	PM_{10} = 50 µg/m^3 (Lags = 0-3 days) Respiratory HA's All age: ER = 8.3% (CI: 5.1, 11.5) 0-4yrs.: ER = 9.9% (CI: 5.4, 14.5) 5-64yrs.: ER = 8.8% (CI: 4.3, 13.4) 65+ yrs.: ER = 9.3% (CI: 5b.1, 13.7) Asthma HA's (all ages) ER = 7.7% (1.0, 14.9) COPD HA's (all ages) ER = 10.0% (5.6, 14.3) Pneumonia and Influenza HA's (all ages) ER = 13.1% (7.2, 19.4)

+ = Used GAM with multiple smooths, but have not yet reanalyzed. * = Used S-Plus Default GAM, and have reanalyzed results.
GAM=Generalized Additive Model, GLM=Generalized Linear Model; NS= Natural Spline, PS=Penalized Spline.

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.3: PM-Respiratory Visits Studies

TABLE 8B-3. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Choudhury et al. (1997) Anchorage, Alaska (90 - 92) Population = 240,000 PM_{10} mean = 41.5 µg/m^3 PM_{10} (SD) = 40.87 PM_{10} maximum=565 µg/m^3	Using insurance claims data for state employees and dependents living in Anchorage, Alaska, number of daily medical visits determined for asthma (mean = 2.42/day), bronchitis, and upper respiratory infections. Used GLM regression, including a time-trend variable, crude season indicator variables (i.e., spring, summer, fall, winter), and a variable for the month following a volcanic eruption in 1992.	Positive association observed between asthma visits and PM_{10}. Strongest association with concurrent-day PM_{10} levels. No co-pollutants considered. Temperature and RH did not predict visits, but did interact with the PM_{10} association. Morbidity relative risk higher with respect to PM_{10} pollution during warmer days.	Asthma Medical Visits (all ages): For mean = 50 µg/m^3 PM_{10} (single poll.) Lag = 0 days ER = 20.9% (CI: 11.8, 30.8)
Lipsett et al. (1997) Santa Clara County, CA Population = NR (Winters 88 - 92) PM_{10} mean = 61.2 µg/m^3 PM_{10} Min/Max = 9/165 µg/m^3	Asthma emergency department (ER) visits from 3 acute care hospitals (mean=7.6/day) related to CoH, NO_2, PM_{10}, and O_3 using Poisson GLM model with long-wave, day of week, holiday, and weather controls (analysis stratified by minimum T). Analyses using GAM also run for comparison. Every other day PM_{10} estimated from CoH. Residential wood combustion (RWC) reportedly a major source of winter PM. Gastro-enteritis (G-E) ER admissions also analyzed as a control disease.	Consistent relationships found between asthma ER visits and PM_{10}, with greatest effect at lower temperatures. Sensitivity analyses supported these findings. For example, .GAM model gave simi.lar, though sometimes less significant, results. NO_2 also associated, but in simultaneous regressions only PM_{10} stayed associated. ER visits for gastroenteritis not significantly associated with air pollution. Results demonstrate an association between wintertime ambient PM_{10} and asthma exacerbations in an area where RWC is a principal PM source.	Asthma ED Visits (all ages) PM_{10} = 50 µg/m^3 (2 day lag): GLM Results: At 20 F, ER = 34.7% (CI: 16, 56.5) At 30 F, ER = 22% (CI: 11, 34.2) At 41 F, ER = 9.1% (CI: 2.7, 15.9)
Norris et al. (1999)+ Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 µg/m^3 PM_{10} IQR = 11.6 µg/m^3 $_{sp}$ mean = 0.4 m 1/10 4 (12.0 µg/m^3 $PM_{2.5}$) $_{sp}$ IQR = 0.3 m 1/10 4 (= 9.5 µg/m^3 $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) were compared with those from lower hospital utilization areas(1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering ($_{sp}$), CO, SO_2, and NO_2 using a semiparametric S-Plus Poisson regression model with spline smooths for season and weather variables, evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. There was no stronger association between ED visits for asthma and air pollution in the higher hospital utilization area than in the lower utilization area in terms of RR's. However, considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city.	Children's (<18 yrs.) Asthma ED Visits Single Pollutant Models: 24h PM_{10} =50 µg/m^3 Lag1 ER = 75.9% (25.1, 147.4) For 25 µg/m^3 $PM_{2.5}$ Lag1 ER = 44.5% (CI: 21.7, 71.4) Multiple Pollutant Models: 24h PM_{10} =50 µg/m^3 Lag1 ER = 75.9% (CI: 16.3, 166) For 25µg/m^3 $PM_{2.5}$ Lag1 ER = 51.2% (CI: 23.4, 85.2)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Norris et al. (2000)+ Spokane, WA (1/95 - 3/97) Population = 300,000 PM_{10} mean. = 27.9 µg/m^3 PM_{10} Min/Max =4.7/186.4 µg/m^3 PM_{10} IQR = 21.4 µg/m^3 Seattle, WA (9/95 - 12/96) Pop. Of Children <18 = 107,816 PM_{10} mean. = 21.5 µg/m^3 PM_{10} Min/Max = 8/69.3 µg/m^3 PM_{10} IQR = 11.7 µg/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yr. (mean=3.2/d) in Spokane and for children <18 yr. (mean=1.8/d) in Seattle. Poisson GAM model applied, controlling for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in both cities. Factor analysis indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with "stagnation" as the "co-pollutant" indicated importance of general air pollution over any single air pollutant index, but not of the importance of various pollutants relative to each other.	<u>Asthma ED Visits</u> Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 50 µg/m^3 Lag 3 ER = 2.4% (CI: -10.9, 17.6) Persons<18 years (Seattle) For PM_{10} IQR = 50 µg/m^3 Lag 3 ER = 56.2% (95 CI: 10.4 , 121.1)
Tolbert et al. (2000b) Atlanta, GA (92 - 94 Summers) Population = 80% of children in total population of 3 million PM_{10} mn. (SE) = 38.9 (15.5) µg/m^3 PM_{10} Range = 9, 105 µg/m^3	Pediatric (<17 yrs. of age) ED visits (mean = 467/day) related to air pollution (PM_{10}, O_3, NO_x, pollen and mold) using GEE and logistic regression and Bayesian models. Autocorrelation, day of week, long-term trend terms, and linear temperature controls included.	Both PM_{10} and O_3 positively associated with asthma ED visits using all three modeling approaches. In models with both O_3 and PM_{10}, both pollutants become non-significant because of high collinearity of the variables (r=0.75).	<u>Pediatric (<17 yrs. of age) ED Visits</u> PM_{10} = 50 µg/m^3 Lag 1 day ER = 13.2% (CI: 1.2, 26.7) With O_3 8.2 (-7.1, 26.1)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} (µg/m^3): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} (µg/m^3): 29.1, 27.6, 12.0 $PM_{2.5}$ (µg/m^3): 19.4, 17.5, 9.35 CP (µg/m^3): 9.39, 8.95, 4.52 10-100 nm PM counts (count/cm^3): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals (µg/m^3): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates (µg/m^3): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity (µg/m^3): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM (µg/m^3): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon (µg/m^3): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for asthma (493), wheezing (786.09) COPD (491, 492, 4966) LRI 466.1, 480, 481, 482, 483, 484, 485, 486), all resp disease (460-466, 477, 480-486, 491, 492, 493, 496, 786.09) for persons 16 yr in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all DVD in period 1 were 6.5 and 28.4, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson GLM regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day-of-week and hospital entry/exit indicators also included. Pollutants	In period 1, observed significant COPD association with 3-day average PM_{10}. COPD was also positively associated with NO_2, O_3, CO and SO_2. No statistically significant association observed between asthma and PM_{10} in period 1. However, asthma positively associated with ozone (p=0.03). In period 2, i.e., the first year of operation of the superstation, no statistically significant associations observed with PM_{10} or $PM_{2.5}$. These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Period 1: PM_{10} (0-2 d): asthma: 5.6% (-8.6, 22.1) COPD: 19.9% (0.1, 43.7) Period 2: (all 0-2 day lag) PM_{10}: asthma 18.8% (-8.7, 54.4) COPD -3.5% (-29.9, 33.0) $PM_{2.5}$: asthma 2.3% (-14.8, 22.7) COPD 12.4% (-7.9, 37.2) $PM_{10-2.5}$: asthma 21.1% (-18.2, 79.3) COPD -23.0% (-50.7, 20.1)
Yang et al (1997) Study Period: 92 - 94 Reno-Sparks, Nevada Population = 298,000 PM_{10} mean = 33.6 µg/m^3 PM_{10} range = 2.2, 157.3 µg/m^3	Association between asthma ER visits (mean = 1.75/d, SD=1.53/d) and PM_{10}, CO and O_3 assessed using linear WLS and ARIMA GLM regression, including adjustments for day-of-week, season, and temperature (but not RH or T-RH interaction). Season adjusted only crudely, using month dummy variable.	Only O_3 showed significant associations with asthma ER visits. However, the crude season adjustment and linear model (rather than Poisson) may have adversely affected results. Also, Beta-gauge PM_{10} mass index used, rather than direct gravimetric mass measurements.	NR

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada			
Delfino et al. (1997) Montreal, Canada Population= 3 million 6-9/92, 6-9/93 1993 Means (SD): PM_{10}= 21.7 µg/m^3 (10.2) $PM_{2.5}$= 12.2 µg/m^3 (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory emergency department (ED) visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using GLM regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons aged 2-64 yrs. For patients >64 yr, O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	Respiratory ED Visits Adults >64: (pollutant lags = 1 day) 50 µg/m^3 PM_{10} ER = 36.6% (10.0, 63.2) 25 µg/m^3 $PM_{2.5}$ ER = 23.9% (4.9, 42.8)
Delfino et al. (1998) Montreal, Canada 6-8/89,6-8/90 Mean PM_{10}= 18.6 µg/m^3 (SD=9.3, 90th% = 30.0 µg/m^3)	Examined the relationship of daily ED visits for respiratory illnesses by age (mean/day: <2yr.=8.9; 2-34yr.=20.1; 35-64yr.=22.6; >64yr.=20.3) with O_3 and estimated $PM_{2.5}$. Seasonal and day-of-week trends, auto-correlation, relative humidity and temperature were addressed in linear time series GLM regressions.	There was an association between $PM_{2.5}$ and respiratory ED visits for older adults (>64), but this was confounded by both temperature and O_3. The fact that $PM_{2.5}$ was estimated, rather than measured, may have weakened its relationship with ED visits, relative to O_3.	Older Adults(>64 yr) Respiratory ED Visits Estimated $PM_{2.5}$ = 25 µg/m^3 Single Pollutant: (lag 1 $PM_{2.5}$) ER = 13.2 (-0.2, 26.6) With Ozone (lag 1 $PM_{2.5}$): Est. $PM_{2.5}$ (lag1) ER = 0.8% (CI: -14.4, 15.8)
Stieb et al. (1996) St. John, New Brunswick, Canada Population = 75,000 May-Sept. 84 - 92 SO_4^{2-} Mean = 5.5 µg/m^3 Range: 1-23, 95th% =14 µg/m^3 TSP Mean = 36.7 µg/m^3 Range:5-108, 95th% =70 µg/m^3	Asthma ED visits (mean=1.6/day) related to daily O_3 and other air pollutants (SO_2, NO_2, SO_4^{2-}, and TSP). PM measured only every 6th day. Weather variables included temperature, humidex, dewpoint, and RH. ED visit frequencies were filtered to remove day of week and long wave trends. Filtered values were GLM regressed on pollution and weather variables for the same day and the 3 previous days.	Positive, statistically significant ($p < 0.05$) association observed between O_3 and asthma ED visits 2 days later; strength of the association greater in nonlinear models. Ozone effect not significantly influenced by addition of other pollutants. However, given limited number of sampling days for sulfate and TSP, it was concluded that "a particulate effect could not be ruled out".	Emergency Department Visits (all ages) Single Pollutant Model 100 µg/m^3 TSP = 10.7% (-66.4, 87.8)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000)+ Saint John, New Brunswick, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 H+ ($nmol/m^3$): 25.7, 36.8 Sulfate ($nmol/m^3$): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for asthma (mean 3.5/day), COPD (mean 1.3/day), resp infections (mean 6.2/day), and all respiratory conditions (mean 10.9/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations were observed between all respiratory ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations were observed with H+, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions.	$PM_{2.5}$, (lag 3) 15.1 (-0.2, 32.8) PM_{10}, (lag 3) 32.5 (10.2, 59.3)
Europe			
Atkinson et al. (1999b) London (92 - 94) Population = NR PM10 Mean = 28.5 $\mu g/m^3$ 10^{th}-90^{th} IQR = 15.8-46.5 $\mu g/m^3$ BS mean =12.7 $\mu g/m^3$ 10^{th}-90^{th} IQR = 5.5-21.6 $\mu g/m^3$	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits from 12 London hospitals considered, but associated population size not reported. Counts for ages 0-14, 15-64, and >64 also examined. Poisson GLM regression used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	PM_{10} positively associated, but not BS, for all-age/all-respiratory category. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship. PM_{10} positively associated for all ages, children, and young adults for asthma ED visits. However, PM_{10}-asthma relationship couldn't be separated from SO_2 in multi-pollutant regressions. Older adult ED visits most strongly associated with CO. No O_3-ED visits relationships found (but no warm season analyses attempted).	PM_{10} (50 $\mu g/m^3$) No co-pollutant: All Respiratory ED visits 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) Asthma ED visits 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 $\mu g/m^3$) 2d lag & co-pollutant: Children's (<15 yrs.) Asthma ED Visits: PM alone: ER = 12.3% (CI: 3.4, 22) &NO_2: ER = 7.8% (CI: -1.2, 17.6) & O_3: ER = 10.5% (CI: 1.6, 20.1) & SO_2: ER = 8.1% (CI: -1.1, 18.2) & CO: ER = 12.1% (CI: 3.2, 21.7)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hajat et al. (1999) London, England (92 - 94) Population = 282,000 PM_{10} mean = 28.2 µg/m^3 PM_{10} 10^{th}-90^{th}%=16.3-46.4 µg/m^3 BS mean = 10.1 µg/m^3 BS 10^{th}-90^{th}%=4.5-15.9 µg/m^3	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care general practitioner asthma and "other LRD" consultations. Asthma consultation means per day = 35.3 (all ages); 14.(0-14 yrs,); 17.7 (15-64 yrs.); 3.6 (>64 yrs.). LRD means = 155 (all ages); 39.7(0-14 yrs,); 73.8 (15-64 yrs.); 41.1 (>64 yrs.). Time-series analyses of daily numbers of consultations performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children. Authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In adults, the authors concluded that the only consistent association was with PM_{10}. Across all of the various age, cause, and season categories considered, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits:</u> 50 µg/m^3 PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 5.4% (CI: -0.6, 11.7) 0-14 yrs.(lg 1): ER = 6.4% (-1.5, 14.6) 15-64 yrs.(lg 0): ER = 9.2% (CI: 2.8, 15.9) >64yrs.(lg 2): ER = 11.7% (-1.8, 26.9) -Year-round, 2 Pollutant, Children (0, 14): (PM_{10} lag = 1 day) PM_{10} ER's: W/NO_2: ER = 0.8% (CI: -8.7, 11.4) W/O_3: ER = 5.5% (-2.1, 13.8) W/SO_2: ER = 3.2% (CI: -6.4, 13.7) <u>Other Lower Resp. Dis. Doctor's Visits:</u> 50 µg/m^3 PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 3.5% (CI: 0, 7.1) 0-14 yrs.(lg 1): ER = 4.2% (CI: -1.2, 9.9) 15-64 yrs.(lg 2): ER= 3.7% (CI: 0.0, 7.6) >64yrs.(lg 2): ER = 6.2% (CI: 0.5, 12.9)
Hajat et al. (2001)+ London (1992-1994) 44,406-49,596 registered patients <1 to 14 years PM_{10} mean 28.5 (13.9)	Daily physician consultations (mean daily 4.8 for children; 15.3 for adults) for allergic rhinitis (ICD-9, 477), SO_2, O_3, NO_2, CO, PM_{10}, and pollen using generalized additive models with nonparametric smoother.	SO_2 and O_3 show strong associations with the number of consultations for allergic rhinitis. Estimates largest for a lag of 3 or 4 days prior to consultations, with cumulative measures stronger than single day lags. Stronger effects were found for children than adults. The two-pollutant analysis of the children's model showed that PM_{10} and NO_2 associations disappeared once either SO_2 or O_3 was incorporated into the model.	PM_{10} - Increment (10-90%) (15.8-46.5) Age <1-14 years lag 3: 10.4 (2.0 to 19.4) Cum 0-3: 17.4 (6.8 to 29.0) Ages 15-64 years lag 2: 7.1 (2.6 to 11.7) Cum 0-6: 20.2 (14.1 to 26.6)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Medina et al. (1997)+ Greater Paris 91 - 95 Population.= 6.5 MM Mean PM_{13} = 25 µg/m^3 PM_{13} min/max = 6/95 µg/m^3 Mean BS = 21 µg/m^3 BS min/max = 3/130 µg/m^3	Evaluated short-term relationships between PM_{13} and BS concentrations and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris. Poisson regression used, with non-parametric smoothing functions controlling for time trend, seasonal patterns, pollen counts, influenza epidemics, day-of-week, holidays, and weather.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results also indicate that air pollutant associations noted for hospital ED visits are also applicable to a wider population that visits their doctor.	Doctor's Asthma House Visits: 50 µg/m^3 PM_{13} Year-round, Single Pollutant: All ages (lg 2): ER = 12.7% (CI: 4.1, 21.9) 0-14 yrs.(lg 0-3): ER = 41.5% (CI: 20, 66.8) 15-64 yrs.(lg 2): ER = 6.3% (CI: -4.6, 18.5)
Damiá et al. (1999) Valencia, Spain (3/94-3/95) Population = NR BS mean = 101 µg/m^3 BS range = 34-213 µg/m^3	Associations of BS and SO_2 with weekly total ED admissions for asthma patients aged > 12 yrs (mean = 10/week) at one hospital over one year assessed, using linear stepwise GLM regression. Season-specific analyses done for each of 4 seasons, but no other long-wave controls. Linear T, RH, BP, rain, and wind speed included as crude weather controls in ANOVA models.	Both BS and SO_2 correlated with ED admissions for asthma (SO_2: r=0.32; BS: r=0.35), but only BS significant in stepwise multiple regression. No linear relationship found with weather variables. Stratified ANOVA found strongest BS-ED association in the autumn and during above average temperatures. Uncontrolled autocorrelation (e.g., within-season) and weather effects likely remain in models.	Asthma ED Visits (all ages): BS = 40 µg/m^3 (single pollutant) BS as a lag 0 weekly average: ER = 41.5% (CI = 39.1, 43.9)
Pantazopoulou et al. (1995) Athens, GR (1988) Population = NR Winter (1/88-3/88,9/88-12/88) BS mean. =75 µg/m^3 BS 5th-95th %=26 - 161 µg/m^3 Summer (3/22/88-3/88,9/21/88) BS mean. =55 µg/m^3 BS 5th-95th %=19 - 90 µg/m^3	Examined effects of air pollution on daily emergency outpatient visits and admissions for cardiac and respiratory causes. Air pollutants included: BS, CO, and NO_2. Multiple linear GLM regression models used, controlling for linear effects of temperature and RH, day of week, holidays, and dummy variables for month to crudely control for season, separately for winter and summer.	Daily number of emergency visits related positively with each air pollutant, but only reached nominal level of statistical significance for NO_2 in winter. However, the very limited time for each within-season analysis (6 mo.) undoubtably limited the power of this analysis to detect significant effects. Also, possible lagged pollution effects were apparently not investigated, which may have reduced effect estimates.	Single Pollutant Models For Winter (BS = 25 µg/m^3) Outpatient Hospital Visits ER = 1.1% (-0.7, 2.3) Respiratory HA's ER = 4.3% (0.2, 8.3) For Summer, BS = 25 µg/m^3) Outpatient Hospital Visits ER = 0.6% (-4.7, 6.0) Respiratory HA's ER = 5.5% (-3.6, 14.7)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Garty et al. (1998) PM_{10} mean 45 µg/m^3 Tel Aviv, Israel (1993)	Seven day running mean of asthma ED visits by children (1-18 yrs.) to a pediatric hospital modeled in relation to PM_{10} in Tel Aviv, Israel.	No PM_{10} associations found with ED visits. The ER visits–pollutant correlation increased significantly when the September peak was excluded. Use of a week-long average and associated uncontrolled long-wave fluctuations (with resultant autocorrelation) likely prevented meaningful analyses of short –term PM associations with ED visits.	N/A
Latin America			
Ilabaca et al. (1999) Santiago, Chile February 1995-August 1996 PM_{10}: warm: 80.3 µg/m^3 cold: 123.9 µg/m^3 $PM_{2.5}$: warm: 34.3 µg/m^3 cold: 71.3 µg/m^3	Number of daily respiratory emergency visits (REVs) related to PM by Poisson GLM model with longer- and short-term trend terms. SO_2, NO_2, O_3.	Stronger coefficients for models including $PM_{2.5}$ than for models including PM_{10} or $PM_{10\text{-}2.5}$. Copollutant effects were significantly associated with REVs. For respiratory patients, the median number of days between the onset of the first symptoms and REV was two to three days. For the majority of patients (70%) this corresponded to the lag observed in this study indicating that the timing of the pollutant effect is consistent with the temporal pattern of REV in this population.	REV, lag 2 Cold $PM_{2.5}$, lag 2 OR: 1.027 (1.01 to 1.04) for a 45 µg/m^3 increment PM_{10}, lag 2 OR: 1.02 (1.01 to 1.04) for a 76 µg/m^3 increment $PM_{2.5}$, lag 2 OR: 1.01 (1.00* to 1.03) for a 32 µg/m^3 increment Pneumonia, lag 2 PM_{10}: 1.05 (1.00* to 1.10) 64 µg/m^3 increment $PM_{2.5}$: 1.04 (1.00* to 1.09) 45 µg/m^3 increment $PM_{10\text{-}2.5}$: 10.5 (1.00* to 1.10) 32 µg/m^3 increment *decimals <1.00

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America (cont'd)			
Lin et al. (1999) Sao Paulo, BR (91-93) Population=NR PM_{10} mean =65 µg/m^3 PM_{10} SD=27 µg/m^3 PM_{10} range=15-193 µg/m^3	Respiratory ED visits by children (0-12 yrs.) To a major pediatric hospital (mean=56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using various GLM models: Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower respiratory (mean = 8/day) and upper respiratory (mean = 9/day) all evaluated. Analyses considered effects of season, day of week, and extreme weather (using T, RH dummy variables).	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants all simultaneously added to the model. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models. More than 20% increase in ED visits found on the most polluted days, "indicating that air pollution is a substantial pediatric health concern".	50 µg/m^3 PM_{10} (0-5-day lag mean) 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/m^3 PM_{10} Min/Max=18.5/380 µg/m^3 PM_{10} IQR = 70.3 – 135.5 µg/m^3	Analysis of daily visits to primary health care clinics for upper (URS) or lower respiratory symptoms (LRS) for children 2-14 yr (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2 yr. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 µg/m^3) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	Lower Resp. Symptoms Clinic Visits PM_{10} = 50 µg/m^3 Single Pollutant Models: -Children<2 years Lag 3 ER = 2.5% (CI: 0.2, 4.8) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.8, 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (CI: 0, 4.4) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.9, 6.5)

DRAFT-DO NOT QUOTE OR CITE

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} 95th5% = 3.26 10 4/m PM_{10} median = 18 µg/m^3 PM_{10} IQR = 11.5-28.8 µg/m^3 PM_{10} 95th% = 92.5 µg/m^3	Study evaluated whether asthma visits to emergency departments (ED) in western Sydney (mean10/day) increased as result of bushfire-generated PM (B_{scatt} from nephelometry) in Jan., 1994 (period 2). Air pollution data included nephelometry (B_{scatt}), PM_{10}, SO_2, and NO_2. Data analyzed using two methods: (1) calculation of the difference in proportion of all asthma ED visits between the time periods, and; (2) Poisson GLM regression analyses. Control variables included T, RH, BP, WS, and rainfall.	No difference found in the proportion of all asthma ED visits during a week of bushfire-generated air pollution, compared with the same week 12 months before, after adjusting for baseline changes over the 12-month period. The max. B_{scatt} reading was not a significant predictor of the daily asthma ED visits in Poisson regressions. However, no long-wave controls applied, other than indep. vars., and the power to detect differences was weak (90% for a 50% difference). Thus, the lack of a difference may be due to low statistical strength or to lower toxicity of particles from burning vegetation at ambient conditions vs. fossil fuel combustion.	ED Asthma Visits (all ages) Percent change between bushfire and non bushfire weeks: PM_{10} = 50 µg/m^3 ER = 2.1% (CI: -0.2, 4.5)
Asia			
Ye et al. (2001) Tokyo, Japan Summer months July-August, 1980-1995 PM_{10} 46.0 mean	Hospital emergency transports for respiratory disease for >65 years of age were related to pollutant levels NO_2, O_3, PM_{10}, SO_2, and CO.	For chronic bronchitis PM_{10} with a lag time of 2 days was the most statistically significant model covariate.	Asthma (ICD-9-493) Coefficienct estimate (SE) 0.003 (0.001)
Chew et al. (1999) Singapore (90 - 94) Population = NR TSP mean = 51.2 µg/m^3 TSP SD = 20.3 µg/m^3 TSP range = 13-184 µg/m^3	Child (3-13 yrs.) ED visits (mean = 12.8/day) and HA's (mean = 12.2/day) for asthma related to levels of SO_2, NO_2, TSP, and O_3 using GLM linear regression with weather, day-of-week controls. Auto-correlation effects controlled by including prior day response variable as a regression variable. Separate analyses done for adolescents (13-21 yrs.) (mean ED=12.2, mean HA=3.0/day).	Positive associations found between TSP, SO_2, and NO_2, and daily HA and ED visits for asthma in children, but only with ED visits among adolescents. Lack of power (low counts) for adolescents' HA's appears to have been a factor in the lack of associations. When ED visits stratified by year, SO_2 and TSP remained associated in every year, but not NO_2. Analyses for control diseases (appendicitis and urinary tract infections) found no associations.	TSP(100 µg/m^3) No co-pollutant: Child (3-13 yrs.)Asthma ED visits Lag 1d ER = 541% (CI: 198.4, 1276.8)

+ = Used GAM with multiple smooths, but have not yet reanalyzed. * = Used S-Plus Default GAM, and have reanalyzed results

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.4: Pulmonary Function Studies

TABLE 8B-4. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	The O_3-ΔPEFR relationship was seen as the strongest.	—
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 $\mu g/m^3$.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	Ozone, SO_2 and sulfate levels low due to low vehicle emissions. PM_{10} associated with change in peak flow.	Lag 0, PM10 average PEF = 0.27 (−0.54, −0.01) per 10 $\mu g/m^3$ increment
Europe			
Gielen et al. (1997) Amsterdam, NL Mean PM_{10} level: 30.5 $\mu g/m^3$ (16, 60.3). Mean maximum 8 hr O_3: 67 $\mu g/m^3$.	Study evaluated 61 children aged 7 to 13 years living in Amsterdam, The Netherlands. 77 percent of the children were taking asthma medication and the others were being hospitalized for respiratory problems. Peak flow measurements were taken twice daily. Associations of air pollution were evaluated using time series analyses. The analyses adjusted for pollen counts, time trend, and day of week.	The strongest relationships were found with ozone, although some significant relationships found with PM_{10}.	Lag 0, PM_{10}: Evening PEF = −0.08 (−2.49, 2.42) Lag 1, PM_{10}: Morning PEF = 1.38 (−0.58, 3.35) Lag 2, PM_{10}: Morning PEF = 0.34 (−1.78, 2.46) Evening PEF = −1.46 (−3.23, 0.32)
Hiltermann et al. (1998) Leiden, NL July-Oct, 1995 O_3, NO_2, SO_2, BS, and PM_{10} ranged from 16.4 to 97.9 $\mu g/m^3$)	270 adult asthmatic patients from an out-patient clinic in Leiden, The Netherlands were studied from July 3 to October 6, 1995. Peak flow measured twice daily. An autoregressive model was fitted to the data. Covariates included temp. and day of week. Individual responses not modeled.	No relationship between ozone or PM_{10} and PFT was found	Lag 0, PM_{10}: Average PEF = −0.80 (−3.84, 2.04) 7 day ave., PM_{10}: Average PEF = −1.10 (−5.22, 3.02)

DRAFT-DO NOT QUOTE OR CITE

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

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Timonen and Pekkanen (1997) Kupio, Finland PM_{10}, BS, NO_2, and SO_2. The intequartile range on PM_{10} was 8 to 23.	Studied 74 asthmatic children (7 to 12 yr) in Kuoio, Finland. Daily mean PEF deviation calculated for each child. Values were analyzed, then using linear first-order autoregressive model. PM was measured using single stage Harvard Impactors.	Lagged concentrations of NO_2 related to declines in morning PEF as well as PM_{10} and BS.	
Penttinen et al. (2001) studied adult asthmatics for 6 months in Helsinki, Findland. PM was measured using a single-stage Harvard impactor. Particle number concentrations were measured using an Electric Aerosol Spectrometer. NO_2PM_{10} ranged from 3.8 to 73.7 $\mu g/m^3$. $PM_{2.5}$ ranged from 2.4 to 38.3 $\mu g/m^3$.	57 asthmatics were followed with daily PEF measurements and symptom and medications diaries from November 1996 to April 1997. PEF deviations from averages were used as dependent variables. Independent variables included PM_1, $PM_{2.5}$, PM_{10}, particle counts, CO, NO, and	The strongest relationships were found between PEF deviations and PM particles below 0.1 µm. No associations were found between particulate pollution and respiratory symptoms.	AM PEF = -.115 (-.448, .218) $PM_{2.5}$ lag one day AM PEF = -.001 (-.334, .332) $PM_{2.5}$ lag two days
Pekkanen et al. (1997) Kuopio, Finland PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 18 $\mu g/m^3$ (10, 23). Mean NO_2 level: 28 $\mu g/m^3$.	Studied 39 asthmatic children aged 7-12 years living in Kuopio, Finland. Changes in peak flow measurements were analyzed using a linear first-order autoregressive model. PM was measured using single stage Harvard impactors.	Changes in peak flow found to be related to all measures of PM, after adjusting for minimum temperature. PN0.032–0.10 ($1/cm^3$) and PN1.0–3.2 ($1/cm^3$) were most strongly associated with morning PEF deviations.	Lag 0, PM_{10}: Evening PEF = –0.35 (–1.14, 0.96) Lag 1, PM_{10}: Morning PEF = –2.70 (–6.65, 1.23) Lag 2, PM_{10}: Morning PEF = –4.35 (–8.02, –0.67) Evening PEF = –1.10 (–4.70, 2.50) Small sized particles had relationships similar to those of PM_{10} for morning and evening PEF.
Segala et al. (1998) Paris, France Nov. 1992 - May 1993. BS, SO_2, NO_2, PM_{13} (instead of PM_{10}), measured. Mean PM_{13} level: 34.2 $\mu g/m^3$ (range 8.8, 95). Mean SO_2 level: 21.7 $\mu g/m^3$ (range 4.4, 83.8). Mean NO_2 level: 56.9 $\mu g/m^3$ (range 23.8, 121.9). PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 years living in Paris, France from Nov. 15, 1992 to May 9, 1993. Peak flow measured three times a day. Covariates in the model included temperature and humidity. An autoregressive model was fitted to the data using GEE methods.	Effects found related to PM_{10} were less than those found related to the other pollutants. The strongest effects were found with SO_2.	Lag 4, PM_{13}: Morning PEF = –0.62 (–1.52, 0.28)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Gauvin et al. (1999) Grenoble, France Summer 1996, Winter 1997 Mean (SD) $\mu g/m^3$ PM_{10} Summer 23 (6.7) PM_{10} Winter 38 (17.3) Sunday 15.55 (5.12) Weekday 24.03 (7.2)	Two panels: mild adult asthmatics, ages 20-60 years, (summer-18 asthmatics, 20 control subjects; winter-19 asthmatics, 21 control subjects) were examined daily for FEV_1 and PEF. Bronchial reactivity was compared Sunday vs. weekday. Temperature and RH controlled.	Respiratory function decreased among asthmatic subjects a few days (lag 2/4 days) after daily PM_{10} levels had increased. Bronchial reactivity was not significantly different between the weekdays and weekends. No copollutant analysis conducted.	For a 10 $\mu g/m^3$ increase in PM_{10} Summer FEV_1 −1.25% (−0.58 to −1.92) PEF −0.87% (−0.1 to −1.63)
Agócs et al. (1997) Budapest, Hungary SO_2 and TSP were measured. TSP was measured by beta reactive absorption methods.	Panel of 60 asthmatic children studied for two months in Budapest, Hungary. Mixed model used relating TSP to morning and evening PEFR measurements, adjusting for SO_2, time trend, day of week, temp., humidity		No significant TSP-PEFR relationships found.
Australia			
Jaulaludin et al. (2000) Sydney, Austrlia 1 February 1994 to 31 December 1994 Six PM_{10} TEOM monitors PM_{10} Mean - 22.8 ±13.9 $\mu g/m^3$ (max 122.8 $\mu g/m^3$)	Population regression and GEE models used a cohort of 125 children (mean age of 9.6 years) in three groups; two with doctor's diagnoses of asthma. This study was designed to examine effects of ambient O_3 and peak flow while controlling for PM_{10}.	In Syndey, O_3 and PM_{10} poorly correlated (0.13). For PM_{10} with O_3, 0.0051 (0.0124) p-0.68 peak flow	PM_{10} only B(SE) = 0.0045 (0.0125) p-0.72 peak flow
Rutherford et al. (1999) Brisbane, Australia PM_{10}, TSP, and particle diameter. PM_{10} ranged form 11.4 to 158.6 $\mu g/m^3$. Particle sizing was done by a Coulter Multisizer.	Study examined effects of 11 dust events on peak flow and symptoms of people with asthma in Brisbane, Australia. PEF data for each individual averaged for a period of 7 days prior to the identified event. This mean was compared to the average for several days of PEF after the event, and the difference was tested using a paired t-test.	The paired t-tests were stat. significant for some days, but not others. No general conclusions could be drawn.	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Latin America			
Romieu et al. (1996) Mexico City, Mexico During study period, maximum daily 1-h O_3 ranged from 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave, PM_{10} levels ranged from 29 to 363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). For 53 percent of study days, PM_{10} levels exceeded 150 $\mu g/m^3$. PM_{10} was measured by a Harvard impactor.	Study of 71 children with mild asthma aged 5-7 years living in the northern area of Mexico City. Morning and evening peak flow measurements recorded by parents. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. Model included terms for minimum temperature.	Ozone strongly related to changes in morning PEF as well as PM_{10}.	Lag 0, PM_{10}: Evening PEF = −4.80 (−8.00, −1.70) Lag 2, PM_{10}: Evening PEF = −3.65 (−7.20, 0.03) Lag 0, $PM_{2.5}$: Evening PEF = −4.27 (−7.12, −0.85) Lag 2, $PM_{2.5}$: Evening PEF = −2.55 (−7.84, 2.74) Lag 1, PM_{10} Morning PEF = −4.70 (−7.65, −1.7) Lag 2, PM_{10} Morning PEF = −4.90 (−8.4, −1.5)
Romieu et al. (1997) Mexico City, Mexico During study period, maximum daily 1-h ozone ranged from 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average ranged from 12 to 126 $\mu g/m^3$. PM_{10} was measured by a Harvard impactor.	Study of 65 children with mild asthma aged 5-13 yr in southwest Mexico City. Morning and evening peak flow measurements made by parents. Peak flow measurements standardized for each person and model was fitted using GEE methods. Model included terms for minimum temperature.	Strongest relationships were found between ozone (lag 0 or 1) and both morning and evening PFT.	Lag 0, PM_{10}: Evening PEF = −1.32 (−6.82, 4.17) Lag 2, PM_{10}: Evening PEF = −0.04 (−4.29, 4.21) Morning PEF = 2.47 (−1.75, 6.75) Lag 0, PM_{10}: Morning PEF = 0.65 (−3.97, 5.32)

DRAFT-DO NOT QUOTE OR CITE

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 SO_2 levels had the strongest effects on asthma symptoms after controlling for subject specific variables and time-dependent confounders.	OR symptom = 1.18 (1.05, 1.33) (PM_{10} same day) OR symptom = 1.17 (1.04, 1.33) (PM_{10} one day lag)
Ostro et al. (2001) studied exacerbation of asthma in African-American children in Los Angeles. PM was measured by a beta-attenuated Andersen monitor. PM_{10} ranged from 21 to 119 $\mu g/m^3$ with a mean of 51.8.	138 children aged 8 to 13 years who had physician diagnosed asthma were included. A daily diary was used to record symptoms and medication use. GEE methods were used to estimate the effects of air pollution on symptoms controlling for meteorological and temporal variables.	Symptoms were generally related to PM_{10} and NO_2, but not to ozone. Reported associations were for pollutant variables lagged 3 days. Results for other lag times were not reported.	24-h OR wheeze = 1.02 (0.99, 106))PM_{10} lag 3 days) OR cough = 1.06 (1.02, 1.09) (PM_{10} lag 3 days) OR shortness of breath = 1.08 (1.02, 1.13) (PM_{10} lag 3 days) 1-h OR cough = 1.05 (1.02, 1.18) lag 3 days

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OFASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Delfino et al. (2002) PM_{10}, ozone, NO_2, fungi, pollen, temperature, relative humidity	22 asthmatic children aged 9-19 were followed March through April of 1996. Study used an asthma symptom score.	No relationship between PM_{10} and symptom score was found	Lag 0 Score OR = 1.17 (0.53, 2.59) 3 Day moving average Score OR = 1.49 (0.71, 2.59) all for 50 $\mu g/m^3$ increase in PM_{10}
Mortimer et al. (2002) Eight U.S. urban areas Daily PM10 were collected in Chicago, Cleveland, and Detroit with an average intra-diary range of 53 $\mu g/m^3$ from the Aerometric Information Retrieval System of EPA.	Study of 846 asthmatic children in the eight urban area National Cooperative Inner City Asthma study. Peak flow and diary symptom data are the outcome measures. Morning symptoms consist of cough, chest tightness, and wheeze. Mixed linear and GEE models were used.	In the three cities with PM_{10} data, a stronger association was seen for PM_{10} than ozone for respiratory symptoms.	Morning symptoms PM_{10} - 2day ave. OR = 1.26 (1.0-1.59)
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate, pollen, daily max temp. measured.	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	Ozone related to respiratory symptoms No relationship between symptoms and other pollutants.	—
Canada			
Vedal et al. (1998) PM_{10} measured by Sierra-Anderson dichotomous sampler PM_{10} range: −1 to 159 $\mu g/m^3$ Port Alberrni British, Columbia	206 children aged 6 to 13 years, 75 with physician's diagnosis of asthma. Respiratory symptom data from diaries, GEE model. Temp., humidity.	PM_{10} associated with respiratory symptoms.	Lag 0 Cough OR = 1.08 (1.00, 1.16) per 10 $\mu g/m^3$ PM_{10} increments
Europe			
Gielen et al. (1997) Amsterdam, NL PM_{10} and ozone. PM_{10} was measured using a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 15 to 60 $\mu g/m^3$.	Study of 61 children aged 7 to 13 years living in Amsterdam, NL. 77 percent were taking asthma medication and the others were being hospitalized for respiratory problems. Respiratory symptoms recorded by parents in diary. Associations of air pollution evaluated using time series analyses, adjusted for pollen counts, time trend, and day of week.	Strongest relationships found with O_3, although some significant relationships found with PM_{10}.	Lag 0, Symptoms: Cough OR = 2.19 (0.77, 6.20) Bronch. Dial. OR = 0.94 (0.59, 1.50) Lag 2, Symptoms: Cough OR = 2.19 (0.47, 10.24) Bronch. Dial. OR = 2.90 (1.80, 4.66)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Hiltermann et al. (1998) Leiden, NL July-Oct 1995. Ozone, PM_{10}, NO_2, SO_2, BS PM_{10} ranged from 16 to 98 μg/m^3 with a mean of 40.	Study of 270 adult asthmatic patients from an out-patient clinic in Leiden, NL from July 3, to October 6, 1995. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data. Covariates included temperature and day of week.	PM_{10}, O_3, and NO_2 were associated with changes in respiratory symptoms.	Lag 0, Symptoms: Cough OR = 0.93 (0.83, 1.04) Short. breath OR = 1.17 (1.03, 1.34) 7 day average, Symptoms: Cough OR = 0.94 (0.82, 1.08) Short. breath OR = 1.01 (0.86, 1.20)
Hiltermann et al. (1997) The Netherlands Ozone and PM_{10} PM_{10} averaged 40 μg/m^3,	Sixty outpatient asthmatics examined for nasal inflammatory parameters in The Netherlands from July 3 to October 6, 1995. Associations of log transformed inflammatory parameters to 24-h PM_{10} analyzed, using a linear regression model. Mugwort-pollen and O_3 were evaluated.	Inflammatory parameters in nasal lavage of patients with intermittent to severe persistent asthma were associated with ambient O_3 and allergen exposure, but not with PM_{10} exposure.	—
Peters et al. (1997a) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 55 μg/m^3 (max 71). Mean SO_2: 100 μg/m^3 (max 383). PM was measured using a Harvard impactor.	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season 1991-1992. Diary used to record presence of cough. Symptom information analyzed using multiple logistic regression analysis.	Weak associations found with 5 day mean sulfates and respiratory symptoms.	Lag 0, PM_{10}: Cough OR = 1.32 (1.16, 1.50) Feeling ill OR = 1.20 (1.01, 1.44) 5 Day Mean, PM_{10}: Cough OR = 1.30 (1.09, 1.55) Feeling ill OR = 1.47 (1.16, 1.86) Lag 0, $PM_{2.5}$: Cough OR = 1.19 (1.07, 1.33) Feeling ill OR = 1.24 (1.09, 1.41) 5 Day Mean, $PM_{2.5}$: Cough OR = 1.02 (0.91, 1.15) Feeling ill OR = 1.21 (1.06, 1.38)
Peters et al. (1997b) Sokolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10}: 47 μg/m^3 (29, 73). Median SO_2: 46 μg/m^3 (22, 88). PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Study of 89 children with asthma in Sokolov, Czech Republic. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. Logistic regression for binary outcomes used. First order autocorrelations were observed and corrected for using polynomial distributed lag structures.	Significant relationships found between TSP and sulfate with both phlegm and runny nose.	Lag 0, Symptoms: Cough OR = 1.01 (0.97, 1.07) Phlegm OR = 1.13 (1.04, 1.23) 5 Day Mean, Symptoms: Cough OR = 1.10 (1.04, 1.17) Phlegm OR = 1.17 (1.09, 1.27)

DRAFT-DO NOT QUOTE OR CITE

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. (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}.
Segala et al. (1998) Paris, France SO_2, NO_2, PM_{13} (instead of PM_{10}), and BS. PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 yr in Paris. Patients followed Nov. 15, 1992 to May 9, 1993. Respiratory symptoms recorded daily in diary. An autoregressive model fitted to data using GEE methods. Covariates included temp. and humidity.	Effects found related to PM_{13} were less than those found related to the other pollutants.	Lag 2, Symptoms: Short. Breath OR = 1.22 (0.83, 1.81) Resp. Infect. OR = 1.66 (0.84, 3.30)
Güntzel et al. (1996) Switzerland SO_2, NO_2, TSP	An asthma reporting system was used in connection with pollutant monitoring in Switzerland from fall of 1988 to fall 1990. A Box-Jenkins ARIMA time series model was used to relate asthma to TSP, O_3, SO_2, and NO_2 after adjusting for temperature.	No significant relationships found.	—
Taggart et al. (1996) Northern England SO_2, NO_2 and BS.	Panel of 38 adult asthmatics studied July 17 to Sept. 22, 1993 in northern England. Used generalized linear model to relate pollutants to bronchial hyper-responsiveness, adjusting for temperature.	Small effects seen in relation to NO_2 and BS.	—
Just et al. (2002) PM_{13}, SO_2, NO_2, O_3	82 medically diagnosed asthmatic children living in Paris, followed for 3 months. Study measured asthma attacks and nocturnal cough, symptoms, and PEF	PM_{13} was only associated with eye irritation.	Lag 0 Asthma episodes OR = 1.34 (0.08, 20.52) for 50 $\mu g/m^3$ PM_{13}.

DRAFT-DO NOT QUOTE OR CITE

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
Von Klot et al. (2002) $PM_{2.5-10}$, PM_{10}, NO_2, SO_2, CO, temperature	53 adult asthmatics in Erfurt, Germany in the winter 1996/1997. Study measured inhaled medication use, wheezing, shortness of breath, phlegm and cough	Medication use and wheezing were associated with $PM_{2.5-10}$	5 Day mean Corticosteroid use OR = 1.12 (1.04-1.20) for 12 $\mu g/m^3$ $PM_{2.5-10}$. Wheezing OR = 1.06 (0.98, 1.15) for 12 $\mu g/m^3$ $PM_{2.5-10}$.
Desqueyroux et al. (2002) PM_{10}, O_3, SO_2, and NO_2	60 severe asthmatic adults in Paris were followed for 13 months. Study measured incident asthma attacks	Attacks were associated with PM_{10} for lags 4 and 5 but not for lags 1, 2, and 3	Lag 1 Attack OR = 0.50 (0.18, 1.34) Lag 2 Attack OR = 0.67 (0.33, 1.47) Lag 3 Attack OR = 1.69 (0.90, 3.18) Lag 4 Attack OR = 2.19 (1.16, 4.16) Lag 5 Attack OR = 2.10 (1.05, 4.32) all for 50 $\mu g/m^3$ increase in PM_{10}
Latin America			
Romieu et al. (1997) Mexico City, Mexico During study period, max daily 1-h O_3 range: 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average range: 12 to 126 $\mu g/m^3$. 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)

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.6: Short-Term PM Exposure Effects On Pulmonary Function in Nonasthmatics

TABLE 8B-6. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Hoek et al. (1998) (summary paper)	Results summarized from several other studies reported in the literature. These included: asymptomatic children in the Utah Valley (Pope et al., 1991), children in Bennekom, NL (Roemer et al., 1993), children in Uniontown, PA (Neas et al., 1995), and children in State College, PA (Neas et al., 1996). Analyses done using a first-order autoregressive model with adjustments for time trend and ambient temp.	Other pollutants not considered.	Significant decreases in peak flow found to be related to PM_{10} increases.
Lee and Shy (1999) North Carolina Mean 24 h PM_{10} conc. over two years: 25.1 μg/m^3.	Study of the respiratory health status of residents whose households lived in six communities near an incinerator in southwestern North Carolina. Daily PEFR measured in the afternoon was regressed against 24 hour PM_{10} level lagged by one day. Results were adjusted for gender, age, height, and hypersensitivity.	PM_{10} was not related to variations in respiratory health as measured by PEFR.	—
Korrick et al. (1998) Mt. Washington, NH O_3 levels measured at 2 sites near top of the mountain. $PM_{2.5}$ measured near base of the mountain. PM was measured by a Harvard impactor.	Study of the effects of air pollution on adult hikers on Mt. Washington, NH. Linear and non-linear regressions used to evaluate effects of pollution on lung function.	$PM_{2.5}$ had no effect on the O_3 regression coefficient.	—
Naeher et al. (1999) Virginia PM_{10}, $PM_{2.5}$, sulfate fraction, H+, and ozone	Daily change in PEF studied in 473 non-smoking women in Virginia during summers 1995-1996. Separate regression models run, using normalized morning and evening PEF for each individual.	Ozone was only pollutant related to evening PEF.	Morning PEF decrements were associated with PM_{10}, $PM_{2.5}$, and H+. Estimated effect from $PM_{2.5}$ and PM_{10} was similar. No PM effects found for evening PEF.
Neas et al. (1996) State College, PA $PM_{2.1}$: mean 23.5; max 85.8 μg/m^3.	Study of 108 children in State College, PA, during summer of 1991 for daily variations in symptoms and PEFRs in relation to $PM_{2.1}$ An autoregressive linear regression model was used. The regression was weighted by reciprocal number of children of each reporting period. Fungus spore conc., temp., O_3 and SO_2 were examined.	Spore concentration associated with deficient in morning PERF.	$PM_{2.1}$ (25 μg/m^3) related to RR of: PM PFER (lag 0) = −0.05 (−1.73, 0.63) PM PEFR (lag 1) = −0.64 (−1.73, 0.44)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Neas et al. (1999) Philadelphia, PA Median PM_{10} level: 31.6 in SW camps, 27.8 in NE camps (IQR ranges of about 18). Median $PM_{2.5}$ level: 22.2 in the SW camps, 20.7 in NE camps (IQR ranges about 16.2 and 12.9, respectively). Particle-strong acidity, fine sulfate particle, and O_3 also measured.	Panel study of 156 normal children attending YMCA and YWCA summer camps in greater Philadelphia area in 1993. Children followed for at most 54 days. Morning and evening deviations of each child's PEF were analyzed using a mixed-effects model adjusting for autocorrelation. Covariates included time trend and temp. Lags not used in the analysis.	Analyses that included sulfate fraction and O_3 separately also found relationship to decreased flow. No analyses reported for multiple pollutant models.	Lag 0, PM_{10}: Morning PEF = -8.16 (−14.81, −1.55) Evening PEF = −1.44 (−7.33, 4.44) 5 day ave, PM_{10} Morning PEF = 2.64 (−6.56, 11.83) Evening PEF = 1.47 (−7.31, 10.22) Lag 0, $PM_{2.5}$ Morning PEF = −3.28 (−6.64, 0.07) Evening PEF = −0.91 (−4.04, 2.21) 5 day ave., $PM_{2.5}$ Morning PEF = 3.18 (−2.64, 9.02) Evening PEF = 0.95 (−4.69, 6.57)
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$) measured. Summary levels not given.	Analyses for 1844 school children in grades 2-5 from six urban areas in eastern U.S. and from separate studies from Uniontown and State College, PA. Lower resp. symptoms, cough and PEF used as endpoints. The authors replicated models used in the original analyses. CM and were used individually and jointly in the analyses. Sulfate fractions also used in the analyses. Details of models not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and, not surprisingly, gave similar answers.	Uniontown Lag 0,$PM_{2.5}$: Evening PEF = −1.52 (−2.80, −0.24) State College Lag 0, $PM_{2.5}$: Evening PEF = −0.93 (−1.88, 0.01) Results presented for CM showed no effect. Results for PM_{10} were not given.
Linn et al. (1996) So. California NO_2 ozone, and PM_5 measured. PM_5 was measured using a Marple low volume sampler PM_5 ranged from 1-145 μg/m^3 with a mean of 24.	Study of 269 school children in Southern California twice daily for one week in fall, winter and spring for two years. A repeated measures analysis of covariance was used to fit an autoregressive model, adjusting for year, season, day of week, and temperature.	Morning FVC was significantly decreased as a function of PM_5 and NO_2	—

DRAFT-DO NOT QUOTE OR CITE

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
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 $\mu g/m^3$.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	No consistent evidence for adverse health effects was seen in the nonasthmatic control group.	—
Europe			
Boezen et al. (1999) Netherlands PM_{10}, BS, SO_2, and NO_2 measured, but methods were not given. PM_{10} ranged from 4.8 to 145 $\mu g/m^3$ 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.	—
Frischer et al. (1999) Austria PM_{10} measured gravimettrically for 14-d periods. Annual mean PM_{10} levels range: 13.6 - 22.9 $\mu g/m^3$. O_3 range: 39.1 ppb - 18.5 pbs between sites.	At nine sites in Austria during 1994, 1995, and 1996, a longitudinal study designed to evaluate O_3 was conducted. During 1994 - 1996, children were measured for FVC, FEV_1 and MEF_{50} six times, twice a year in spring and fall. 1060 children provided valid function tests. Mean age 7.8 ± 0.7 yr. GEE models used. PM_{10}, SO_2, NO_2, and temp. evaluated.	Small but consistent lung function decrements in cohort of school children associated with ambient O_3 exposure.	PM_{10} showed little variation in exposure between study site. For PM_{10}, positive effect seen for winter exposure but was completely confounded by temperature. PM_{10} Summertime $\beta = 0.003$ SE 0.012 p=0.77
Grievink et al. (1999) Netherlands PM_{10} and BS. PM_{10} ranged from 12 to 123 $\mu g/m^3$ with a mean of 44.	A panel of adults with chronic respiratory symptoms studied over two winters in The Netherlands starting in 1993/1994. Logistic regression analysis was used to model the prevalence of large PEF decrements. Individual linear regression analysis of PEF on PM was calculated and adjusted for time trends, influenza incidence, and meteorological variables.	Subjects with low levels of serum β-carotene more often had large PEF decrements when PM_{10} levels were higher, compared with subjects with high serum β-carotene. Results suggested serum β-carotene may attenuate the PM effects on decreased PEF.	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Künzli et al. (2000)	Ackermann-Liebrich et al. (1997) data reanalyzed. Authors showed that a small change in FVC (-3.14 percent) can result in a 60% increase in number of subjects with FVC less than 80 percent of predicted.	The results were for two hypothetical communities, A and B.	—
Roemer et al. (2000) PM_{10} means for 17 panels ranged 11.2 to 98.8 μg/m^3. SO_2, NO_2, and elemental content of PM also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Separate results reported by endpoints included symptoms as reported in a dairy and PEF. Individual panels were analyzed using multiple linear regression analysis on deviations from mean PEF adjusting for auto-correlation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	PM_{10} analyses not focus of this paper.
Scarlett et al. (1996) PM_{10}, O_3, and NO_2 measured.	In study of 154 school children, pulmonary function was measured daily for 31 days. Separate autoregressive models for each child were pooled, adjusting for pollen, machine, operator, time of day, and time trend.	PM_{10} was related to changes in FEV and FVC	—
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured.	Panel study of 795 children aged 7 to 11 years, with and without chronic respiratory symptoms living in urban and nonurban areas in the Netherlands. Peak flow measured for three winters starting in 1992/1993. Peak flow dichotomized at 10 and 20% decrements below the individual median. Number of subjects was used as a weight. Minimum temperature day of week, and time trend variables were used as covariates. Lags of 0, 1 and 2 days were used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No multiple pollutant models analyses reported.	Lag 0, PM_{10}, Urban areas Evening PEF OR = 1.15 (1.02, 1.29) Lag 2, PM_{10}, Urban areas Evening PEF OR = 1.07 (0.96, 1.19) 5 day ave, PM_{10}, Urban areas Evening PEF = 1.13 (0.96, 1.32)

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (2000) Netherlands PM_{10} averages ranged 24 to 53 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured. PM_{10} was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of 489 adults aged 50-70 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Resp. symptoms and peak flow measured for three winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Peak flow dichotomized at 10 and 20% decrements below the individual median. The number of subjects used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	BS tended to have the most consistent relationship across endpoints. Sulfate fraction also related to increased respiratory effects. No analyses reported for multiple pollutant models. Relationship found between PM_{10} and the presence of 20% decrements in symptomatic subjects from urban areas.	Lag 0, PM_{10}, Urban areas Morning large decrements OR = 1.44 (1.02, 2.03) Lag 2, PM_{10}, Urban areas Morning large decrements OR = 1.14 (0.83, 1.58) 5 day ave, PM_{10}, Urban areas Morning large decrements OR = 1.16 (0.64, 2.10) Results should be viewed with caution because of problems in analysis.
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$ level: 15 (25^{th}, 75^{th} percentiles = 9, 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in the spring of 1995 in Kuopio, Finland. Morning and evening deviations of each child's PEF analyzed, using a general linear model estimated by PROC MIXED. Covariates included a time trend, day of week, temp., and humidity. Lags of 0 through 3 days were used, as well as a 4-day moving average. Various fine particles were examined.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly. Effects varied by lag. Separating effects by size was difficult.	Lag 0, PM_{10}: Morning PEF = 1.21 (−0.43, 2.85) Evening PEF = 0.72 (−0.63, 1.26) 4 day ave, PM_{10} Morning PEF = −1.26 (−5.86, 3.33) Evening PEF = 2.33 (−2.62, 7.28) Lag 0, $PM_{2.5}$ Morning PEF = 1.11 (−0.64, 2.86) Evening PEF = 0.70 (−0.81, 2.20) 4 day ave., $PM_{2.5}$ Morning PEF = −1.93 (−7.00, 3.15) Evening PEF = 1.52 (−3.91, 6.94)

DRAFT-DO NOT QUOTE OR CITE

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.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 µg/m^3 PM_{10} (25 µg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured. Details on monitoring methods and pollutant ranges were not given.	Study of 40 subjects aged over 55 years with COPD living in Christchurch, New Zealand conducted during winter of 1994. Subjects recorded their peak flow measurements. A log-linear regression model with adjustment for first order auto-correlation was used to analyze peak flow data and a Poisson regression model was used to analyze symptom data.	Few significant associations found between the health endpoints and the pollutants.	Lag 0, PM_{10}: PEF = –0.86 (–2.33, 0.61)
Jalaludin et al. (2000) studied PEF in 148 children 6 primary schools in Sydney, Australia. PM was measured by tapered element oscillating microbalance. Mean PM_{10} was 22.8 +- 13.9 µg/m^3.	148 children in grades 3-5 were followed for 11 months, recording PEF twice daily. The normalized change in PEF was analyzed using GEE methods. PEF was related to SO_3, PM_{10}, NO_2, as well as meteorological variables.	Daily mean deviations in PEF were related to ozone, but no relationships were found with PM_{10} or NO_2. Multiple pollutant models gave similar results to those given by the single pollutant models.	Change from AM to PM PEF = 0.045 (–.205, 2.95) lag one day
Asia			
Chen et al. (1999) Taiwan Beta-gauge PM_{10} ranged 44.5 to 189.0 µg/m^3 for peak concentrations.	In 3 Taiwan communities in 1995, PM_{10} by B-gauge measured at selected primary schools in each community. Spirometry tests (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, PEF) obtained in period May 1995 to Jan. 1996 using ATS protocol in study pop. aged 8 to 13 yr. 895 children were analyzed. Study was designed to investigate short-term effect of ambient air pollution in cross-sectional survey. Multivariate linear model analysis used in both one pollutant and multipollutant models, with 1-, 2-, and 7-day lags. SO_2, CO, O_3, NO_2 and PM_{10} examined, as were meteorol. variables.	In the one-pollutant model, daytime peak O_3 conc. with a 1-day lag significantly affected both FVC and FEV_1. NO_2, SO_2, CO affected FVC. PM_{10} showed nonsignificant decrement. No significant result demonstrated in the model for the exposure with 7 days lag. In the multi-pollutant model, only peak O_3 conc. with 1-day lag showed sig. effect on FVC and $FEV_{1.0}$.	One pollutant model daytime average PM_{10} – 2 day lag FVC –0.37 se 0.39
Tan et al. (2000) Southeast Asian smoke-haze event 9/29 – 10/27 1997 PM_{10} mean daily was 125.4 ± 44.9 µg/m^3 ultra range of 47 to 216 µg/m^3 in Singapore	Examined the association between acute air pollution caused by biomass burning and peripheral UBC counts in human serial measurement made during the event were compared with a period after the haze cleared (Nov. 21 – Dec. 5, 1997)	Indices of atmospheric pollution were significantly associated in the elevated band neutrophil counts expressed as a percentage of total polymonphonuclear leukocytes (PMN). No statistically significant difference in FEU_1 and FUC were observed during and after haze exposure.	

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.7: Short-Term PM Exposure Effects On Symptoms in Nonasthmatics

TABLE 8B-7. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 µg/m^3 PM_{10} (25 µg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$ by substation).. Summary levels not given	Reported on analysis of 1844 school children in grades 2–5 from six urban areas in the eastern U.S., and from separate studies from Uniontown and State College, PA. Lower respiratory symptoms, and cough used as endpoints. The authors replicated the models used in the original analyses. CM and $PM_{2.5}$ were used individually and jointly in the analyses. Sulfates fractions were also used in the analyses. Details of the models were not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and not surprisingly gave similar answers.	$PM_{2.5}$ was found to be significantly related to lower respiratory symptoms even after adjusting for CM, whereas the reverse was not true. However, for cough, CM was found to be significantly related to lower respiratory symptoms even after adjusting for $PM_{2.5}$, whereas the reverse was not true.
Zhang et al. (2000) Vinton, Virginia 24- h PM_{10}, $PM_{2.5}$, sulfate and strong acid measured in 1995.	In southwestern Virginia, 673 mothers were followed June 10 to Aug. 31, 1995 for the daily reports of present or absence of runny or stuffy nose. PM indicator, O_3, NO_2 temp., and random sociodemographic characteristics considered.	Of all pollutants considered, only the level of coarse particles as calculated (PM_{10} - $PM_{2.5}$) independently related to incidence of new episode of runny noses.	—
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 µg/m^3.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	No consistent evidence for adverse health effects was seen in the nonasthmatic control group.	—
Long et al. (1998) Winnepeg, CN PM_{10}, TSP, and VOC measured. Methods for PM monitoring not given. Ranges of values also not given.	Study of 428 participants with mild airway obstruction conducted during a Winnepeg pollution episode. Gender specific odds ratios of symptoms were calculated for differing PM_{10} levels using the Breslow-Day test.	Cough, wheezing, chest tightness, and shortness of breath were all increased during the episode	—
Europe			
Boezen et al. (1998) Amsterdam, NL PM_{10}, SO_2, and NO_2 measured. PM_{10} ranged from 7.9 to 242.2 µg/m^3 with a median of 43.	Study of 75 symptomatic and asymp. adults near Amsterdam for three months during winter 1993-1994. An autoregressive logistic model was used to relate PM_{10} to respiratory symptoms, cough, and phlegm, adjusting for daily min. temp., time trend, day of week.	No relationship found with pulmonary function. Some significant relationships with respiratory disease found in subpopulations	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Howel et al. (2001) study of children's respiratory health in 10 non-urban communities of northern England. PM levels were measured using a single continuous real-time monitor. PM_{10} levels ranged from 5 to 54 μg/m^3.	The study included 5 pairs of non-urban communities near and not so near 5 coal mining sites. 1405 children aged 1-11 years were included. 275 of the children reported having asthma. Diaries of respiratory symptoms were collected over a 6 week period. PM_{10}, measured by a single continuous real-time monitor, ranged from 5 to 54 μg/m^3.	The associations found between daily PM_{10} levels and respiratory symptoms were frequently small and positive and sometimes varied by community.	OR wheeze = 1.16 (1.05, 1.28 (PM_{10}) OR cough = 1.09 (1.02, 1.16) (PM_{10}) OR reliever use = 1.00 (0.94, 1.06) (PM_{10})
Roemer et al. (1998) Mean PM_{10} levels measured at local sites ranged 11.2 to 98.8 μg/m^3 over the 28 sites.	Pollution Effects on Asthmatic Children in Europe (PEACE) study was a multi-center study of PM_{10}, BS, SO_2, and NO_2 on respiratory health of children with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Children with chronic respiratory symptoms were selected into the panels. The symptom with one of the larger selection percentages was dry cough (range over sample of study communities 29 to 92% [22/75; 84/91] with most values over 50%). The group as a whole characterized as those with chronic respiratory disease, especially cough.	These studies modeled group rates and are an example of the panel data problem.	—
Roemer et al. (2000) PM_{10} means for the 17 panels ranged 11.2 to 98.8 μg/m^3. SO_2, NO_2, and PM elemental content also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Endpoints included symptoms as reported in a dairy and PEF. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	The analysis of PM_{10} was not a focus of this paper.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured.	A panel study of 795 children aged 7 to 11 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Respiratory symptoms measured for 3 winters starting 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. The number of subjects was used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No analyses reported with multiple pollutant models.	Lag 0, PM_{10}, Urban areas Cough OR = 1.04 (0.95, 1.14) Lag 2, PM_{10}, Urban areas Cough OR = 0.94 (0.89, 1.06) 5 day ave, PM_{10}, Urban areas Cough OR = 0.95 (0.80, 1.13)
van der Zee et al. (2000) Netherlands Daily measurements of PM_{10}, BS, fine sulfate, nitrate, ammonium and strong acidity. PM_{10} was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of adults aged 50 to 70 yr during 3 consecutive winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. Analysis treated as a time series, adjusting for first order autocorrelation. Number of subjects used as a weight. Min. temp., day of week, time trend variables used as covariates. Lags 0, 1 and 2 days used, as well as 5 day moving average.	BS was associated with upper respiratory symptoms.	Lag 0, Symptoms, Urban areas LRS OR = 0.98 (0.89, 1.08) URS OR = 1.04 (0.96, 1.14) Lag 2, Symptoms, Urban areas LRS OR = 1.01 (0.93, 1.10) URS OR = 1.04 (0.96, 1.13) 5 day ave, Symptoms, Urban areas LRS OR = 0.95 (0.82, 1.11) URS OR = 1.17 (1.00, 1.37)
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$: 15 (25^{th} and 75^{th} percentiles of 9 and 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in spring 1995 in Kuopio, Finland. Cough, phlegm, URS, LRS and medication use analyzed, using a random effects logistic regression model (SAS macro GLIMMIX). Covariates included a time trend, day of week, temp., and humidity. Lags of 0 to 3 days used, as well as 4-day moving average.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly.	Lag 0, PM_{10}: Cough OR = 1.00 (0.87, 1.16) 4 day ave, PM_{10} Cough OR = 1.58 (0.87, 2.83) Lag 0, $PM_{2.5}$ Cough OR = 1.04 (0.88, 1.23) 4 day ave., $PM_{2.5}$ Cough OR = 2.01 (1.04, 3.89)
Keles et al. (1999) Istanbul, Turkey Nov. 1996 to Jan. 1997. TSP levels ranged from annual mean of 22 μg/m^3 in unpolluted area to 148.8 μg/m^3 in polluted area.	Symptoms of rhinitis and atopic status were evaluated in 386 students grades 9 and 10 using statistical package for the social sciences, Fisher tests, and multiple regression model as Spearman's coefficient of correlation.	No difference found for atopic status in children living in area with different air pollution levels.	—

DRAFT-DO NOT QUOTE OR CITE

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	—

DRAFT-DO NOT QUOTE OR CITE

Appendix 8B.8: Long-Term PM Exposure Effects On Respiratory Health Indicators, Symptoms, and Lung Function

TABLE 8B-8. LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States			
Abbey et al. (1998) California Communities 20 year exposure to respirable particulates, suspended sulfates, ozone, and PM_{10}. PM_{10} ranged from 1 to 145 µg/m^3 with a mean value of 32.8.	Sex specific multiple linear regressions were used to relate lung function measures to various pollutants in long-running cohort study of Seven Day Adventists (ASHMOG Study).	Sulfates were associated with decreases in FEV.	Frequency of days where PM_{10} > 100 µg/m^3 associated with FEV decrement in males whose parents had asthma, bronchitis, emphysema, or hay fever. No effects seen in other subgroups.
Berglund et al.. (1999) California communities	Cohort study of Seventh Day Adventists. Multivariate logistic regression analysis of risk factors (e.g., PM) for chronic airway disease in elderly non-smokers, using pulmonary function test and respiratory symptom data.	Significant risk factors identified: childhood respiratory illness, reported ETS exposure, age, sex and parental history.	For PM_{10} > 100µg/m^3, 42 d/yr: RR = –1.09 CT (0.92, 1.30) for obstructive disease determined by pulmonary function tests.
Peters et al. (1999a,b) 12 southern California communities 5 year exposure to PM_{10}, ozone, NO_2, acid levels. PM_{10} annual averages ranged from 13 to 70 µg/m^3.	Asthma, bronchitis, cough and wheeze rates were adjusted for individual covariates. Community rates were then regressed on pollutant averages for 1986-1990.	Wheeze was associated with NO_2 and acid levels. No symptoms were associated with PM_{10} levels.	OR for PM_{10} (per 25 µg/m^3): Asthma 1.09 (0.86, 1.37) Bronchitis 0.94 (0.74, 1.19) Cough 1.06 (0.93, 1.21) Wheeze 1.05 (0.89, 1.25)
Avol et al. (2001) Subjects living in Southern California in 1993 that moved to other western locations in 1998. Pollutants O_3, NO_2, PM_{10} differences 15 to 66 µg/m^3.	Studied 110 children who were 10 yrs of age at enrollment and 15 at follow-up who had moved from communities filled out health questions and underwent spirometry. Linear regression used to determine whether annual average change in lung function correlated with average changes in PM.	As a group, subjects who moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with a higher PM_{10} showed decreased growth in lung function.	PM_{10} 24 hr average PERF ml/s per 10 µg/m^3 mean = –34.9 95% CI –59.8, –10.1
Gauderman et al. (2000) 12 So. California communities 1993 to 1997 Pollutants: O_3, NO_2, PM_{10}, and $PM_{2.5}$. PM_{10} levels ranged from 16.1 to 67.6 µg/m^3 across the communities.	Studies of lung function growth of 3035 children in 12 communities within 200-mile radius of Los Angeles during 1993 to 1997. Cohorts of fourth, seventh, and tenth-graders studied. By grade cohort, a sequence of linear regression models were used to determine over the 4yr of follow-up, if average lung function growth rate of children was associated with average pollutant levels. Adjustment were made for height, weight, body mass index, height by age interaction, report of asthma activity or smoking. Two-pollutant models also used.	Lung growth rate for children in most polluted community, as compared to least polluted, was estimated to result in cumulative reduction of 3.4% in FEV_1 and 5.0% in MMEF over 4-yr study period. Estimated deficits mostly larger for children spending more time outdoors. Due to the high correlation in concentrations across communities, not able to separate effects of each pollutant. No sig. associations seen with O_3.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates were: –0.85% for PM_{10} (p = 0.026); –0.64% for $PM_{2.5}$ (p = 0.052); –0.90% for $PM_{10-2.5}$ (p = 0.030); –0.77% for NO_2 (p = 0.019); and –0.73% for inorganic acid vapor (p = 0.042).

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
Gauderman et al. (2002) Follow-up on 12 southern California communities 5 year exposure to PM_{10}, ozone, NO_2, acid levels. PM_{10} annual averages ranged from 5 to 27 $\mu g/m^3$.	Linear regression analysis was used to estimate the individual lung function growth adjusted for height, weight, body mass index, and smoking. Growth rates were then adjusted for individual covariates to obtain community adjusted growth rates. These rates were then related to pollutant averages for 1996-1999.	Lung function growth was related to total acid.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates of FEV1 were: PM_{10} −0.21 (−1.04, 0.64), ozone −0.55 (−1.27, 0.16), NO_2 −0.48 (−1.12, 0.17), $PM_{2.5}$ −0.39 (−1.06, 0.28), total acid −0.63 (−1.21, 0.17)
McConnell et al. (1999) 12 Southern California communities 1994 air monitoring data. PM_{10} (mean 34.8; range 13.0 - 70.7 $\mu g/m^3$). $PM_{2.5}$ (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)
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.	—

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
Raizenne et al. (1996) 24 communities in the U.S. and Canada Pollutants measured for at least one year prior to lung function tests: PM_{10}, $PM_{2.1}$, particle strong acidity, O_3, NO_2, and SO_2. PM was measured with a Harvard impactor. For pollutant ranges, see Dockery et al. (1996).	Cross-sectional study of lung function. City specific adjusted means for FEV and FVC calculated by regressing the natural logarithm of the measure on sex, ln height, and ln age. These adjusted means were then regressed on the annual pollutant means for each city.	PM measures (e.g., particle strong acidity) associated with FEV and FVC decrement.	—
Europe			
Ackermann-Liebrich et al. (1997) Eight Swiss regions Pollutants: SO_2, NO_2, TSP, O_3, and PM_{10}. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 53 µg/m^3 with a mean of 37.	Long-term effects of air pollution studied in cross-sectional population-based sample of adults aged 18 to 60 yrs. Random sample of 2,500 adults in each region drawn from registries of local inhabitants. Natural logarithms of FVC and FEV_1 regressed against natural logarithms of height, weight, age, gender, atopic status, and pollutant variables.	Significant and consistent effects on FVC and FEV were found for PM_{10}, NO_2 and SO_2.	Estimated regression coefficient for PM_{10} versus FVC = −0.035 (95% CI −0.041, −0.028). Corresponding value for FEV_1 −0.016 (95% CI −0.023 to −0.01). Thus, 10 µg/m^3 PM_{10} increase estimated to lead to estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.
Braun-Fahrländer et al. (1997) 10 Swiss communities Pollutants: PM_{10}, NO_2, SO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 µg/m^3.	Impacts of long-term air pollution exposure on respiratory symptoms and illnesses were evaluated in cross-sectional study of Swiss school children, (aged 6 to 15 years). Symptoms analyzed using a logistic regression model including covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others.	Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The colinearity of the pollutants including NO_2, SO_2, and O_3, prevented any causal separation.	PM_{10} Chronic cough OR 11.4 (2.8, 45.5) Bronchitis OR 23.2 (2.8, 45.5) Wheeze OR 1.41 (0.55, 3.58)
Zemp et al. (1999) 8 study sites in Switzerland. Pollutants: TSP, PM_{10}, SO_2, NO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 µg/m^3 with a mean of 21.	Logistic regression analysis of associations between prevalences of respiratory symptoms in random sample of adults and air pollution. Regressions adjusted for age, BMI, gender, parental asthma, education, and foreign citizenship.	Chronic cough and chronic phlegm and breathlessness were related to TSP, PM_{10} and NO_2.	Chronic cough, chronic phlegm and breathlessness were related to PM_{10}, and TSP.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Heinrich et al. (1999) Bitterfeld, Zerbstand Hettstedt areas of former East Germany, During Sept. 1992 to July 1993 TSP ranged from 44 to 65 µg/m^3; PM_{10} measured October 1993 - March 1994 ranged from 33 to 40; and BS ranged from 26 to 42 µg/m^3. PM was measured with a Harvard impactor.	Parents of 2470 school children (5-14 yr) completed respiratory health questionnaire. Children excluded from analysis if had lived < 2 years in their current home, yielding an analysis group of 2,335 children. Outcomes studied: physician diagnosis for asthma, bronchitis, symptom, bronchial reactivity, skin prick test, specific IgE. Multiple logistic regression analyses examined regional effects.	Controlling for medical, socio-demographic, and indoor factors, children in more polluted area had circa 50% increase for bronchitic symptoms and physician-diagnosed allergies compared to control area and circa twice the respiratory symptoms (wheeze, shortness of breath and cough). Pulmonary function tests suggested slightly increased airway reactivity to cold for children in polluted area.	No single pollutant could be separated out as being responsible for poor respiratory health.
Heinrich et al. (2000) Three areas of former E. Germany Pollution measures: SO_2, TSP, and some limited PM_{10} data. TSP decreased from 65, 48, and 44 µg/m^3 to 43, 39, and 36 µg/m^3 in the three areas. PM was measured with a Harvard impactor.	Cross-sectional study of children (5-14 yr). Survey conducted twice, in 1992-1993 and 1995-1996; 2,335 children surveyed in first round, and 2,536 in second round. Only 971 children appeared in both surveys. The frequency of bronchitis, otitus media, frequent colds, febrile infections studied. Because changes measured over time in same areas, covariate adjustments not necessary.	PM and SO_2 levels both decreased in the same areas; so results are confounded.	The prevalence of all respiratory symptoms decreased significantly in all three areas over time.
Heinrich et al. (2002) Surveyed children aged 5-14 in 1992-3, 1995-6, 1998-9. Annual TSP levels ranged from 25-79 µg/m^3. Smallparticles ($NC_{0.01-2.5}$ per $10^3 cm^{-3}$) remained relatively constant.	A two-stage logistic regression model was used to analyze the data which adjusted for age, gender, educational level of parents, and indoor factors. The model included fixed area effects, random deviations, and errors from the adjustments. Parameters were estimated using GEE methods.	The study found bronchitis and frequency of colds were significantly related to TSP.	An increment of 50 µg/m^3 TSP was associated with an odds ratio for bronchitis of 3.02 (1.72-5.29) and an odds ratio of 1.90 (1.17-3.09) for frequency of colds.
Krämer et al. (1999) Six East and West Germany communities (Leipzig, Halle, Maddeburg, Altmark, Duisburg, Borken) Between 1991 and 1995 TSP levels in six communities ranged from 46 to 102 µg/m^3. Each East Germany community had decrease in TSP between 1991 and 1995. TSP was measured using a low volume sampler.	The study assessed relationship between TSP and airway disease and allergies by parental questionnaires in yearly surveys of children (5-8 yr) between February and May. The questions included pneumonia, bronchitis ever diagnosed by physician, number of colds, frequent cough, allergic symptoms. In all, 19,090 children participated. Average response was 87%. Analyses were conducted on 14,144 children for whom information on all covariates were available. Variables included gender; parent education, heating fuel, ETS. Logistic regression used to allow for time trends and SO_2 and TSP effects. Regression coefficients were converted to odds ratios.	TSP and SO_2 simultaneously included in the model. Bronchitis ever diagnosed showed a significant association. A decrease in raw percentage was seen between the start of the study and the end for bronchitis. Bronchitis seemed to be associated only with TSP in spite of huge differences in mean SO_2 levels.	Bronchitis ever diagnosed TSP per 50 µg/m^3 OR 1.63 CI (1.37 – 1.93) Halle (East) TSP µg/m^3 — % Bronchitis 1991 102 — 60.5 1992 73 — 54.7 1993 62 — 49.6 1994 52 — 50.4 1995 46 — 51.9

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Baldi et al. (1999) 24 areas of seven French towns 1974-1976 Pollutants: TSP, BS, and SO_2, NO_4 3-year average TSP-mean annual values ranging 45-243 µg/m^3. TSP was measured by the gravimetric method.	Reanalysis of Pollution Atmospheric of Affection Respiratory Chroniques (PAARC) survey data to search for relationships between mean annual air pollutant levels and prevalence of asthma in 1291 adult (25-59 yrs) and 195 children (5-9 yrs) asthmatics. Random effects logistic regression model used and included age, smoking, and education level in the final model.	Only an association between SO_2 and asthma in adults observed. No other pollutant was associated. Nor was relationship with children seen. Meteorological variables and O_3 not evaluated.	For a 50 µg/m^3 increase in TSP Adult asthma prevalence OR 1.01 CI 0.92–1.11 SO_2 Adult asthma prevalence OR 1.26 CI 1.04–1.53
Zeghnoun et al. (1999) La Havre, France during 1993 and 1996. Daily mean BS levels measured in three stations ranged 12 - 14 µg/m^3.	Respiratory drug sales for mucolytic and anticough medications (most prescribed by a physician) were evaluated versus BS, SO_2, and NO_2 levels. An autoregressive Poisson regression model permitting overdispersion control was used in the analysis.	Respiratory drug sales associated with BS, NO_2, and SO_2 levels. Both an early response (0 to 3 day lag) and a longer one (lags of 6 and 9 days) were associated.	—
Leonardi et al. (2000) 17 cities of Central Europe Yearly average concentration (Nov. 1995 - Oct. 1996) across the 17 study areas varied from 41 to 96 µg/m^3 for PM_{10}, from 29 to 67 µg/m^3 for $PM_{2.5}$, and from 12 to 38 µg/m^3 for $PM_{10\text{-}2.5}$.	Cross-sectional study collected blood and serum samples from 10-61 school children aged 9 to 11 in each community 11 April to 10 May 1996. Blood and serum samples examined for parameters in relation to PM. Final analysis group of 366 examined for peripheral lymphocyte type and total immunoglobulin classes. Association between PM and each log transformed biomarker studied by linear regression in two-stage model with adjustment for confounding factors (age, gender, number of smokers in house, laboratory, and recent respiratory illness). This survey was conducted within the frame work of the Central European study of Air Quality and Respiratory Health (CEASAR) study.	Number of lymphocytes (B, $CD4^+$, $CD8^d$, and NK) increased with increasing concentration of PM adjusted for confounders. The adjusted regression slopes are largest and statistically significant for $PM_{2.5}$ as compared to PM_{10}, but small and non statistically signif. for $PM_{10\text{-}2.5}$. Positive relationship found between concentration of IgG in serum and $PM_{2.5}$ but not for PM_{10} or $PM_{10\text{-}2.5}$. Two other models produced similar outcomes: a multi-level linear regression model and an ordinal logistic regression model.	Adjusted Regression slope $PM_{2.5}$ $CD4^+$ 80% 95% CI (34; 143) $p < 0.001$ Total IgG 24% 95% CI (2; 52) p 0.034

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Turnovska and Kostiranev (1999) Dimitrovgrad, Bulgaria, May 1996 Total suspended particulate matter (TSPM) mean levels were 520 ± I 61 µg/m^3 in 1986 and 187 ± 9 µg/m^3 in 1996. SO_2, H_2S, and NO_2 also measured.	Respiratory function of 97 schoolchildren (mean age 10.4 ± 0.6 yr) measured in May 1996 as a sample of 12% of all four-graders in Dimitrovgrad. The obtained results were compared with reference values for Bulgarian children aged 7 to 14 yr, calculated in the same laboratory in 1986 and published (Gherghinova et al., 1989; Kostianev et al., 1994). Variation analysis technique were used to treat the data.	Vital capacity and FEV_1 were significantly lower (mean value. = 88.54% and 82.5% respectfully) comparing values between 1986 and 1996. TSPM pollution had decreased by 2.74 times to levels still higher than Bulgarian and WHO standards.	—
Jedrychowski et al. (1999) In Krakow, Poland in 1995 and 1997 Spacial distributions for BS and SO_2 derived from network of 17 air monitoring stations. BS 52.6 µg/m ± 53.98 in high area and 33.23 ± 35.99 in low area.	Effects on lung function growth studied in preadolescent children. Lung function growth rate measured by gain in FVC and FEV_1 and occurrence of slow lung function growth (SLFG) over the 2 yr period defined as lowest quintile of the distribution of a given test in gender group. 1129 children age 9 participated in first year and 1001 in follow-up 2 years later. ATS standard questionnaire and PFT methods used. Initially univariate descriptive statistics of pulmonary function indices and SLFG were established, followed by multivariate linear regression analyses including gender, ETS, parental education, home heating system and mold. SO_2 also analyzed.	Statistically significant negative association between air pollution level and lung function growth (FVC and FEV_1) over the follow up in both gender groups. SLFG was significantly higher in the more polluted areas only among boys. In girls there was consistency in the direction of the effect, but not stat. significant. Could not separate BS and SO_2 effects on lung function growth. Excluding asthma subjects subsample (size 917) provided similar results.	<u>Boys</u> SLFG (FVC) OR = 2.15 (CI 1.25 – 3.69) SLFG (FEV_1) OR = 1.90 (CI 1.12 – 3.25) <u>Girls</u> FVC OR = 1.50 (CI 0.84 – 2.68) FEV1 OR = 1.39 (CI 0.78 – 2.44)
Jedrychowski and Flak (1998) In Kracow Poland, in 1991-1995 Daily 24 h concentration of SPM (black smoke) measured at 17 air monitoring stations. High areas had 52.6 µg/m^3 mean compared to low areas at 33.2 µg/m^3.	Respiratory health survey of 1,129 school children (aged 9 yr). Respiratory outcomes included chronic cough, chronic phlegm, wheezing, difficulty breathing and asthma. Multi-variable logistic regression used to calculate prevalence OR for symptoms adjusted for potential confounding.	The comparison of adjusted effect estimates revealed chronic phlegm as unique symptom related neither to allergy nor to indoor variable but was associated significantly with outdoor air pollution category (APL). No potential confounding variable had major effect.	It was not possible to assess separately the contribution of the different sources of air pollutants to the occurrence of respiratory symptoms. ETS and household heating (coal vs. gas vs. central heating) appeared to be of minimal importance.
Horak et al. (2002) Frischer et al. (1999) Eight communities in lower Austria between 1994-1997. PM_{10} mean summer value of 17.36 µg/m^3 and winter value of 21.03 µg/m^3.	Lung function assessed in 975 school children in grade 2-3. A several step analysis included GEE and sensitivity analyses.	Concluded that long term exposure to PM_{10} had a significant negative effect on lung function with additional evidence for a further effect for O_3 and NO_2.	After adjusting for confounders an increase in PM_{10} by 10 µg/m^3 was associated with a decrease in FEV_1 growth at 84 mL/yr and 329 mL/5 yr for MEF_{25-75}.

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Gehring et al. (2002) In Munich, Germany December 1997 - January 1999 Annual $PM_{2.5}$ levels determined by 40 sites and a GIS predictor for model. Mean $PM2^{.5}$ annual average of 13.4 $\mu g/m^3$ with range of 11.90 to 21.90 $\mu g/m^3$	Effect of traffic-related air pollutants. $PM_{2.5}$ and NO_2 on respiratory health outcomes wheeze, cough, bronchitis, respiratory infections, and runny nose were evaluated using multiple logistic regression analyses of l, 756 children during the first and second year of life adjusting for potential confounding factors.	There was some indication of an association between $PM_{2.5}$ and symptoms of cough but not other outcomes. In the second year of life most effects were attenuated.	—
Latin America			
Calderón-Garcidueñas et al. (2000) Southwest Metropolitan Mexico City (SWMMC) winter of 1997 and summer of 1998.	Study of 59 SWMMC children to evaluate relationship between exposure to ambient pollutants (O_3 and PM_{10}) and chest x-ray abnormalities. Fishers exact test used to determine significance in a 2x2 task between hyperinflation and exposure to SWMMC pollutant atmosphere and to control, low-pollutant city atmosphere.	Bilateral symmetric mild lung hyperinflation was significantly associated with exposure to the SWMMC air pollution mixture ($p>0.0004$). This raises concern for development of chronic disease outcome in developing lungs.	—
Australia			
Lewis et al. (1998) Summary measures of PM_{10} and SO_2 estimated for each of 10 areas in steel cities of New South Wales. PM_{10} was measured using a high volume sampler with size-selective inlets.	Cross-sectional survey of children's health and home environment between Oct 1993 and Dec 1993 evaluated frequency of respiratory symptoms (night cough, chest colds, wheeze, and diagnosed asthma). Covariates included parental education and smoking, unflued gas heating, indoor cats, age, sex, and maternal allergy. Logistic regression analysis used allowing for clustering by GEE methods.	SO_2 was not related to differences in symptom rates, but adult indoor smoking was.	Night cough OR 1.34 (1.18, 1.53) Chest colds OR 1.43 (1.12, 1.82) Wheeze OR 1.13 (0.93, 1.38)
Asia			
Wong et al. (1999b) Hong Kong, 1989 to 1991 Sulfate concentrations in respirable particles fell by 38% after implementing legislation reducing fuel sulfur levels.	3405 nonsmoking, women (mean age 36.5 yr; SD ± 3.0) in a polluted district and a less polluted district were studied for six respiratory symptoms via self-completed questionnaires. Binary latent variable modeling used.	Comparison was by district; no PM measurements reported. Results suggest control regulation may have had some (but not statistically significant) impact.	—

DRAFT-DO NOT QUOTE OR CITE

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: B – 119.79, SE 28.17, t – 4.25, $p < 0.01$ FVC: B – 57.89, SE 30.80, t – 1.88, $p < 0.05$

DRAFT-DO NOT QUOTE OR CITE

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Zhang et al. (1999) 4 areas of 3 Chinese Cities (1985 - 1988) TSP levels ranged from an annual arithmetic mean 137 $\mu g/m^3$ to 1250 $\mu g/m^3$ using gravimetric methods.	A pilot study of 4 districts of 3 Chinese cities 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 $\mu g/m^3$. SO_2 and NO_2 measurements were also available. TSP was measured gavimetrically.	Pilot cross-sectional survey of 2789 elementary school children in four Chinese communities chosen for their PM gradient. Frequency of respiratory symptoms (cough, phlegm, wheeze, and diagnosed asthma, bronchitis, or pneumonia) assessed by questionnaire. Covariates included parental occupation, education and smoking. The analysis used logistic regression, controlling for age, sex, parental smoking, use of coal in home, and home ventilation.	Results not directly related to pollution levels, but symptom rates were highest in highest pollution area for cough, phlegm, hospitalization for respiratory disease, bronchitis, and pneumonia. No gradient correlating with pollution levels found for the three lower exposure communities.	—

DRAFT-DO NOT QUOTE OR CITE

9. INTEGRATIVE SYNTHESIS

9.1 INTRODUCTION

This chapter focuses on integration of key information 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). It also highlights key findings on environmental effects of airborne PM.

9.1.1 Legislative Requirements and Past NAAQS Reviews

As indicated in U.S. Code (1991), the U.S. Clean Air Act (CAA), Sections 108 and 109 (42 U.S.C. Sections 7408 and 7409) govern the establishment, review, and revision of National Ambient Air Quality Standards (NAAQS). Section 108(a) directs the EPA Administrator to list pollutants, which, in the Administrator's judgement, cause or contribute to air pollution which may reasonably be anticipated to endanger either public health or welfare and to issue air quality criteria for them. The air quality criteria are to reflect the latest scientific information useful in indicating the kind and extent of all identifiable effects on public health and welfare that may be expected from the presence of the pollutant in ambient air. Section 109 directs the EPA Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants identified under Section 108. Section 109(b)(1) defines a primary standard as a level of air quality, the attainment and maintenance of which, in the judgement of the Administrator, based on the criteria and allowing for an adequate margin of safety, is requisite to protect the public health. Section 109(b)(2) defines a secondary standard as one which, in the judgement of the Administrator, based on the criteria, is requisite to protect public welfare from any known or anticipated adverse effects associated with the presence of such pollutants. Welfare effects include, but are not limited to, effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and personal comfort and

well-being. Section 109(d) requires periodic review and, as appropriate, revision of existing criteria and standards. It also requires an independent committee of non-EPA experts, the Clean Air Scientific Advisory Committee (CASAC), to provide advice and recommendations to the EPA Administrator regarding the scientific soundness and appropriateness of criteria and NAAQS for PM and other "criteria air pollutants" (i.e., O_3, NO_2, SO_2, CO, and Pb) regulated under CAA Sections 108-109.

EPA first promulgated primary and secondary NAAQS for PM on April 30, 1971 (Federal Register, 1971). These standards measured PM as "total suspended particulate" (TSP), which refers to ambient PM up to a nominal size of 25 to 45 micrometers (μm). The primary standards for PM (measured as TSP) were 260 $\mu g/m^3$ (24-h average), not to be exceeded more than once per year, and 75 $\mu g/m^3$ (annual geometric mean). The secondary standard (measured as TSP) was 150 $\mu g/m^3$ (24-h average), not to be exceeded more than once per year. In July 1987, EPA revised the 1971 standards to protect against adverse health effects of inhalable airborne particles which can be deposited in the lower (thoracic) regions of the human respiratory tract, with "PM_{10}" as the indicator, i.e., those particles collected by a sampler with a specified penetration curve yielding an upper 50% cut-point of 10-μm aerodynamic diameter (Federal Register, 1987). EPA established identical primary and secondary PM_{10} standards for two averaging times: 150 $\mu g/m^3$ (24-h average), with no more than one expected exceedance per year and 50 $\mu g/m^3$ (expected annual arithmetic mean), averaged over three years.

Taking into account information and assessments presented in the 1996 PM AQCD and associated 1996 PM Staff Paper (SP), advice and recommendations of CASAC, and public comments received on proposed revisions to the PM NAAQS (Federal Register, 1996), the EPA Administrator promulgated significant revisions to the PM NAAQS in July 1997 (Federal Register, 1997). In that decision, although it was determined that the PM NAAQS should continue to focus on particles less than or equal to 10 μm in diameter, it was also determined that the fine and coarse fractions of PM_{10} should be considered separately. New standards were added, using $PM_{2.5}$ as the indicator for fine particles, and PM_{10} standards were retained for the purpose of regulating coarse-fraction particles. Two new $PM_{2.5}$ standards were set: an annual standard of 15 $\mu g/m^3$, based on the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations from single or multiple community-oriented monitors; and a 24-hour standard of 65 $\mu g/m^3$, based on the 3-year average of the 98th percentile of 24-hour $PM_{2.5}$ concentrations at

each population-oriented monitor within an area. To continue to address coarse-fraction particles, the annual PM_{10} standard was retained, and the form, but not the level, of the 24-hour PM_{10} standard was revised to be based on the 99th percentile of 24-hour PM_{10} concentrations at each monitor in an area. The secondary standards were revised by making them identical in all respects to the primary standards.

Following 1997 promulgation of the revised PM NAAQS, legal challenges were filed by many parties, addressing a broad range of issues. In May 1998, the U.S. Court of Appeals for the District of Columbia Circuit issued an initial opinion upholding EPA's decision to establish fine particle standards, finding that such standards were amply justified by the growing body of empirical evidence showing a relationship between fine particle pollution and adverse health effects. Further, the court found "ample support" for EPA's decision to regulate coarse fraction particles, although it vacated the revisions to the 1987 PM_{10} standards on the basis of PM_{10} being a "poorly matched indicator for coarse particulate pollution" because PM_{10} includes fine particles. As a result of this aspect of the court's ruling, which EPA did not appeal, the 1987 PM_{10} standards remain in effect. In addition, the U.S. Court of Appeals initially broadly held that EPA's approach to establishing the level of the standards in its 1997 decisions on both the PM and ozone NAAQS (which were promulgated on the same day and considered together by the court in this aspect of its opinion) effected "an unconstitutional delegation of legislative authority." EPA appealed this aspect of the court's ruling to the U.S. Supreme Court. In February 2001, the U.S. Supreme Court unanimously reversed the Court of Appeals' ruling on the constitutional issue, and sent the case back to the Court of Appeals for resolution of any remaining issues not addressed in that court's earlier rulings. In March 2002, the Court of Appeals rejected all remaining challenges to the standards, finding that the 1997 $PM_{2.5}$ standards were reasonably supported by the record and were not "arbitrary or capricious." American Trucking Associations v. EPA, 283 F. 3d 355, 369-72 (D.C. Cir. 2002). Thus, the 1997 $PM_{2.5}$ standards are in effect.

This updated revision of the PM AQCD, then, focuses on assessment of extensive newly available (since the 1996 PM AQCD) information pertinent to consideration of (a) possible retention or revision of the $PM_{2.5}$ NAAQS set to protect mainly against health effects related to exposures to ambient (outdoor) concentrations of airborne fine-mode particles now experienced in the United States; (b) the possible setting of new primary standards to protect against thoracic

coarse fraction ($PM_{10-2.5}$) health effects; and (c) possible revisions to PM secondary standards to protect against PM-related welfare effects.

9.1.2 Organization of the Chapter

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. This chapter first provides background information on key features of atmospheric particles, highlighting important distinctions between fine and coarse 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 particles should be treated as two distinct subclasses of air pollutants. Recent data for the 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 selected U.S. urban airsheds are also summarized to place the ensuing human exposure and health effects discussions in perspective. After discussing human exposure aspects, the chapter next summarizes key points regarding respiratory tract dosimetry, followed by a discussion of the extensive PM health database that has expanded greatly during recent years.

The latter includes numerous new epidemiologic studies of populations throughout the world published since the 1996 PM AQCD that provide further evidence that notable health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM found in contemporary U.S. urban air sheds. Epidemiologic findings related to specific PM components (by size, chemical composition) and source contributions are also noted. Evaluations of other possible explanations for the reported PM epidemiology results (e.g., other co-pollutants, choice of models, etc.) also are discussed, ultimately leading to the conclusion that the reported associations of PM exposure and effects are valid. Quantitative evidence is also discussed that (a) further substantiates associations of such serious health effects with U.S. ambient PM_{10} levels, (b) also more strongly establishes fine particles (as indexed by various indicators, e.g., $PM_{2.5}$) as likely being important contributors to the observed human health effects, and (c) now provides additional information on associations between thoracic coarse particles (as indexed by $PM_{10-2.5}$) and adverse health impacts. The overall coherence of the newer epidemiologic database also is discussed.

New toxicologic evidence (derived from controlled exposure studies of humans and laboratory animals) is also highlighted, which elucidates findings on mechanisms of action and other information that greatly enhances the plausibility of the epidemiologic findings in comparison to 1996. The nature of the observed effects and the biological mechanisms that might underlie such effects then are discussed, including with regard to effects seen in compromised laboratory animal models meant to mimic features thought to contribute to increased risk for susceptible human subpopulations. The increased, but still limited, availability of new experimental evidence necessary to evaluate or directly substantiate the viability of hypothesized mechanisms is noted. Information concerning possible contributions of particular classes of specific ambient PM constituents also is summarized.

The chapter also provides information on the identification of susceptible human population groups at special risk for ambient PM effects and factors placing them at increased risk, which need to be considered in generating risk estimates for the possible occurrence of PM-related health events in the United States. In addition, the chapter also makes note of new information related to estimation of potential life-shortening attributable to PM effects.

As such, the overall sequencing of topics covered in the chapter is basically organized to follow the risk assessment framework shown in Figure 9-1, along with some additional information being provided by which to place current findings in perspective in relation to some potential public health implications for U.S. population groups. The information presented here and overall in this revised PM AQCD will provide key inputs to development of a PM Staff Paper and associated exposure and risk analyses being developed by EPA's Office of Air Quality Planning and Standards (OAQPS) to support consideration of options for possible retention or revision of the primary PM NAAQS. In addition, information highlighted at the end of this chapter and discussed in more detail in Chapter 4 with regard to environmental effects of ambient PM will provide inputs to OAQPS analyses supporting considerations related to secondary PM NAAQS.

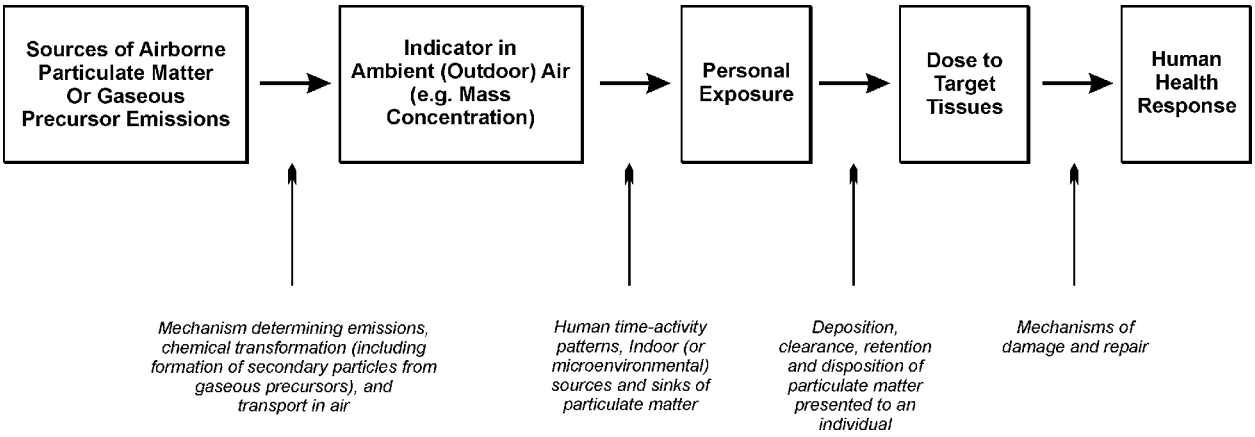

Figure 9-1. A general framework for integrating particulate-matter research. Note that this figure is not intended to represent a framework for research management. Such a framework would include multiple pathways for the flow of information.

Source: National Research Council (2001), as modified from NRC (1983, 1994), Lioy (1990), and Sexton et al. (1992).

9.2 BACKGROUND

9.2.1 Basic Concepts

Atmospheric particles originate from a variety of sources and possess a range of morphological, chemical, physical, and thermodynamic properties. Sources include combustion, photochemical oxidation of precursors, and soil dust. Atmospheric particles contain inorganic ions, metallic compounds, elemental carbon, organic compounds, and crustal compounds. Some atmospheric particles are hygroscopic and contain particle-bound water. The organic fraction is especially complex, containing hundreds of organic compounds. Individual particles may be composed of any number of the above and other components.

9.2.2 Particle Size Distributions

As discussed in Chapter 2, the distribution of particles with respect to size is an important physical parameter governing their behavior. Atmospheric particles vary in density and often are not spherical. Therefore, their diameters are often described by an "equivalent" diameter (i.e., that of a unit density sphere that would have the same physical behavior). Diffusion and

gravitational settling are important physical behaviors for particle transport, collection, and removal processes, including deposition in the respiratory tract. Different equivalent diameters are used depending on which process is more important. For smaller particles diffusion is more important and the Stokes diameter, D_p, is often used. For a smooth, spherically shaped particle, D_p exactly equals the physical diameter of the particle. For irregularly shaped particles, D_p is the diameter of an equivalent sphere that would have the same aerodynamic resistance. For larger particles gravitational setting is more important and the aerodynamic diameter, D_a, is often used. D_a depends on the density of the particle and is defined as the diameter of a spherical particle with a density of 1 g/cm^3 but with a settling velocity equal to that of the particle in question. The atmospheric deposition rates of particles, and therefore, their residence times in the atmosphere, are a strong function of their diameters. The diameter also influences deposition patterns of particles within the lung. The effects of atmospheric particles on visibility, radiative balance, and climate, will also be influenced by the size distribution of the particles. Atmospheric particles cover several orders of magnitude in particle size. Therefore, size distributions often are expressed in terms of the logarithm of the particle diameter on the X-axis and the measured differential concentration on the Y-axis. If the differential concentration is plotted on a linear scale, the number of particles (per cm^3 of air), or the surface area, the volume, or the mass of particles (per m^3 of air) having diameters in the size range from log D to log(D + ΔD), will be proportional to the area under that part of the size distribution curve.

Averaged atmospheric size distributions are shown in Figures 9-2. Figure 9-2a shows the number distributions of particles, on a logarithmic scale, as a function of particle diameter for several aerosols. The particle volume distributions for two of these are shown in Figure 9-2b. These distributions show that most of the particles are quite small, below 0.1 μm; whereas most of the particle volume (and therefore most of the mass) is found in particles larger than 0.1 μm.

9.2.3 Definitions of Particle Size Fractions

Aerosol scientists use three different approaches or conventions in the classification of particles by size: (1) modes, based on the observed size distributions and formation mechanisms; (2) cut point, usually based on the 50% cut point of the specific sampling device, including legally specified, regulatory sizes for air quality standards; and (3) dosimetry or

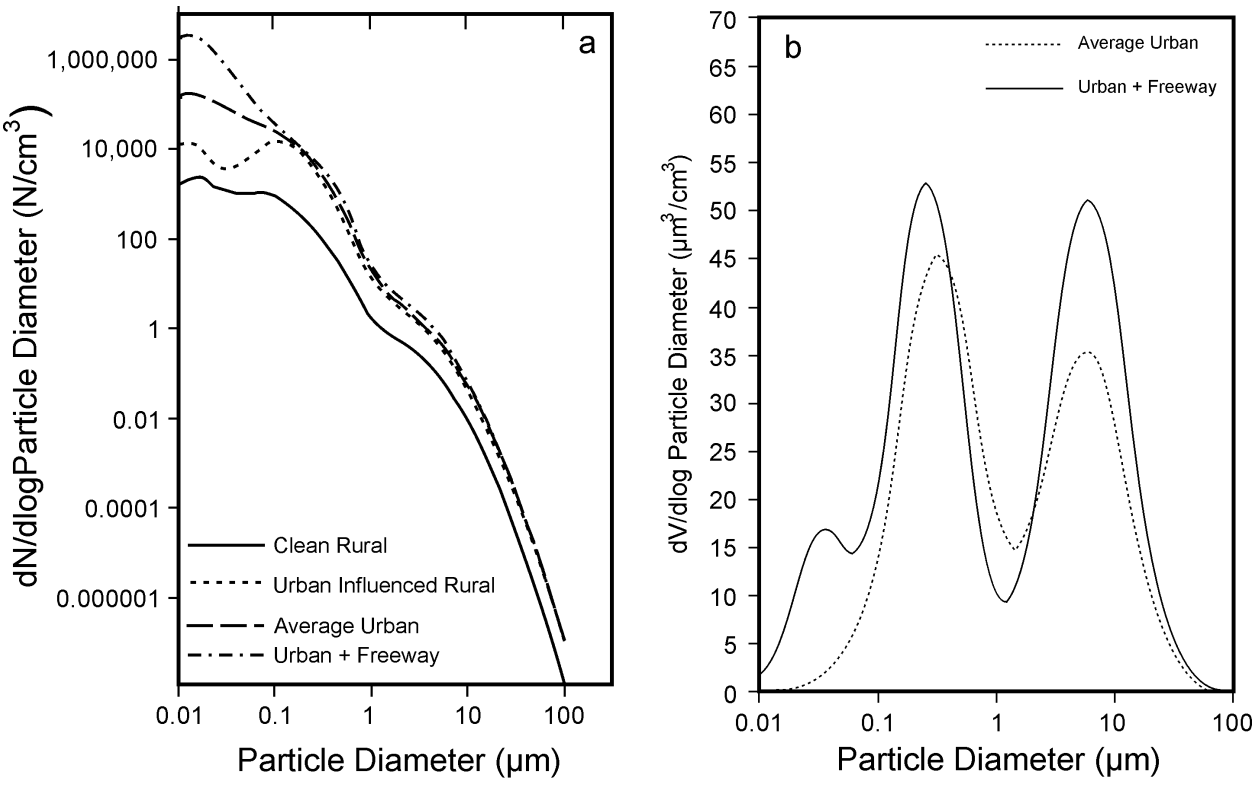

Figure 9-2. Particle size distributions: (a) number of particles as a function of particle diameter: number concentrations are shown on a logarithmic scale to display the wide range by site and size and (b) particle volume as a function of particle diameter: for the averaged urban and freeway-influenced urban number distributions shown in Figure 2-1 of Chapter 2.

Source: Whitby and Sverdrup (1980).

occupational health sizes, based on the entrance into various compartments of the respiratory system.

Modal. The modal classification, first proposed by Whitby (1978), is shown in Figure 9-3. New modes introduced since 1978 are shown in Figure 9-4. The nucleation and Aitkin modes are best observed in the number distribution. The observed modal structure is frequently approximated by several log-normal distributions. Terms used in the modal description of particle size distributions are defined as follows. *Nucleation Mode:* Freshly formed particles with diameters below 10 nm, observed during active nucleation events. The lower limit, where

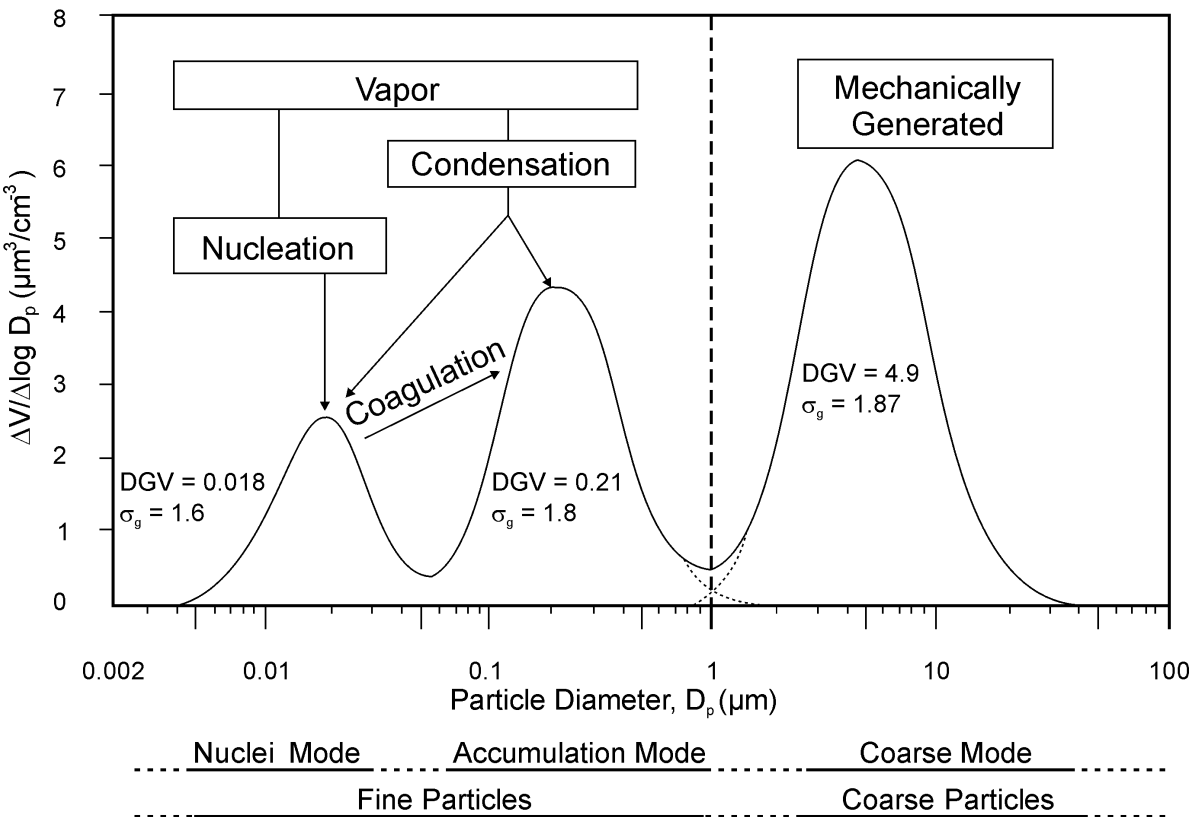

Figure 9-3. Volume size distribution, measured in traffic, showing fine and coarse particles and the nuclei and accumulation modes within the fine particles. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and σ_g (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).

Source: Adapted from Wilson and Suh (1997).

particles and large molecules overlap, is uncertain. Current techniques limit measurements to particles 3 nm or greater. *Aitkin Mode:* Larger particles with diameters between 10 and 100 nm. The Aitken mode may result from growth of smaller particles or nucleation from higher concentrations of precursors. Nucleation and Aitkin nuclei modes are normally observed in the number distribution. *Accumulation Mode*: Particles with diameters from about 0.1 µm to just above the minimum in the mass or volume distributions which usually occurs between 1 and 3 µm. Accumulation-mode particles normally do not grow into the coarse mode.

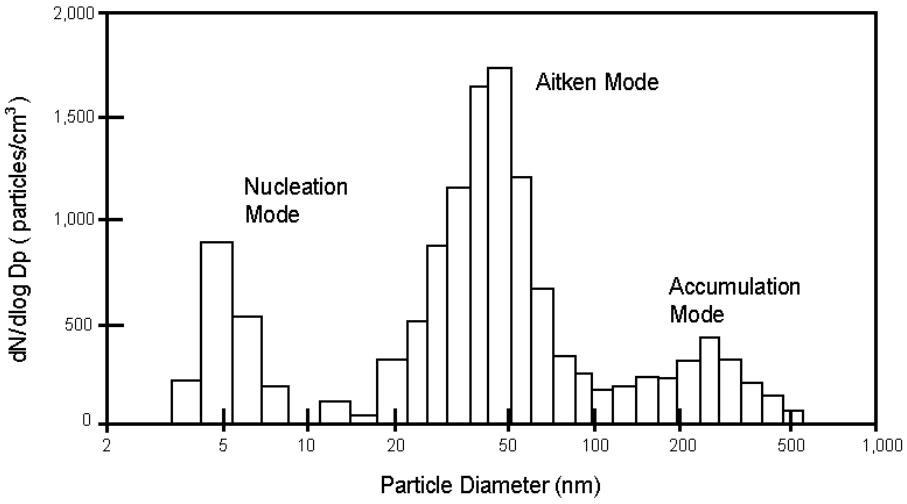

Figure 9-4. Submicron number size distribution observed in a boreal forest in Finland showing the tri-modal structure of fine particles. The total particle number concentration was 1011 particles/cm^3 (10 minute average).

Source: Mäkelä et al. (1997).

Nucleation-mode and Aitkin-mode particles grow by coagulation (two particles combining to form one) or by condensation (low-equilibrium vapor pressure gas molecules condensing on a particle) and "accumulate" in this size range. *Coarse Mode or Coarse Particles:* Particles with diameters mostly greater than the minimum in the particle mass or volume distributions, which generally occurs between 1 and 3 μm. These particles are usually formed by mechanical breakup of larger particles or bulk material. *Fine Particles:* Fine particles include the nucleation, Aitkin, and accumulation modes, i.e., particles from the lowest measurable size, currently about 3 nm, to just above the minimum in the mass or volume distribution which generally occurs between 1 and 3 μm. These particles are generated during combustion or formed from gases. *Ultrafine Particles*: That portion of fine particles with diameters below about 0.1 μm (100 nm), i.e., the Aitkin and nucleation modes.

Modes are defined primarily in terms of their formation mechanisms but also differ in terms of sources, composition, age, and size. The major processes that influence the formation and growth of particles are also shown in Figure 9-3. New particles may be formed by nucleation from gas phase material. Particles may grow by condensation as gas phase material

condenses on existing particles. Particles also may grow by coagulation as two particles combine to form one. Nucleation mode applies to newly formed particles which have had little chance to grow by condensation or coagulation. Aitkin mode particles are also recently formed particles that are still actively undergoing coagulation. However, because of higher concentrations of precursors or more time for condensation and coagulation, the particles have grown to larger sizes. Accumulation mode applies to the final stage as particles, originally formed as nuclei, grow to a point where growth slows down. Gas phase material condenses preferentially on smaller particles and the rate constant for coagulation of two particles decreases as the particle size increases. Therefore, nucleation-mode particles grow into the Aitkin mode and further into the accumulation mode, but accumulation-mode particles do not normally grow into the coarse mode. The nucleation, Aitkin, and accumulation modes, which together are called fine particles, are formed primarily by combustion or chemical reactions of gases yielding products with low saturated vapor pressures. Fine particles include metals and elemental and organic carbon (primary PM) and sulfate, nitrate, ammonium ions, and organic compounds (secondary PM).

The coarse mode refers to particles formed by mechanical breakdown of minerals, crustal material, and organic debris. The composition includes primary minerals and organic material. The accumulation mode and the coarse mode overlap in the region between 1 and 3 μm (and occasionally over an even larger range). In this region, chemical composition of individual particles can usually, but not always, allow identification of a source or formation mechanism and so permit identification of a particle as belonging to the accumulation or coarse mode.

Over the years, the terms fine and coarse, as applied to particle sizes, have lost the precise meaning given in Whitby's (1978) definition. In any given article, therefore, the meaning of fine and coarse, unless defined, must be inferred from the author's usage. In particular, $PM_{2.5}$ and fine particles are not equivalent because $PM_{2.5}$ includes some particles between about 1 and 2.5 μm D_a from the small-size tail of the coarse mode.

Sampler Cut Point. Another set of definitions of particle size fractions arises from considerations of size-selective sampling. Size-selective sampling refers to the collection of particles below or within a specified aerodynamic size range. Size fractions are usually specified by the 50% cut point size; e.g., $PM_{2.5}$ refers to particles collected by a sampling device that

collects 50% of 2.5 μm particles and rejects 50% of 2.5 μm particles. However, size fractions are defined, not merely by the 50% cut point, but by the entire penetration curve. Examples of penetration curves are given in Figure 9-5. Thus, as shown by Figure 9-5, a $PM_{2.5}$ sampler, as defined by the Federal Reference Method, rejects 94% of 3 μm particles, 50% of 2.5 μm particles, and 16% of 2 μm. Samplers with the same 50% cut point but differently shaped penetration curves would collect different fractions of PM. Size-selective sampling has arisen in an effort to measure particle size fractions with some special significance (e.g., health, visibility, source apportionment, etc.), to measure mass size distributions, or to collect size-segregated particles for chemical analysis. Dichotomous samplers split the particles into smaller and larger fractions that may be collected on separate filters. However, some fine particles ($\approx$10%) are collected with the coarse particle fraction. Cascade impactors use multiple size cuts to obtain a distribution of size cuts for mass or chemical composition measurements. One-filter samplers with a variety of upper size cuts are also used, e.g., $PM_{2.5}$, PM_{10}.

Regulatory size cuts are a specific example of size-selective sampling. As noted earlier, the NAAQS for PM were revised in 1987 to use PM_{10}, rather than total suspended particulate matter (TSP), as the indicator for the PM NAAQS (Federal Register, 1987). The use of PM_{10} as an indicator is an example of size-selective sampling based on a regulatory size cut (Federal Register, 1987). The selection of PM_{10} as an indicator was based on health considerations and was intended to focus regulatory concern on those particles small enough to enter the thoracic region of the human respiratory tract. The $PM_{2.5}$ standard set in 1997 is also an example of size-selective sampling based on a regulatory size cut (Federal Register, 1997). The $PM_{2.5}$ standard was based primarily on epidemiologic studies using concentrations measured with $PM_{2.5}$ samplers as an exposure index. However, the $PM_{2.5}$ sampler was not designed to collect respirable particles. It was designed to collect fine particles. EPA is currently considering the possibility of a thoracic coarse particle standard with $PM_{10-2.5}$ as an indicator. Examples of regulatory size cuts are shown in Figure 9-6. Note also that, in the range of particle aerodynamic diameter (D_a) between 1.0 and 2.5 μm, there is overlap between fine and coarse particles. The degree of overlap depends on prevailing conditions of humidity and the amount of soil dust in the atmosphere.

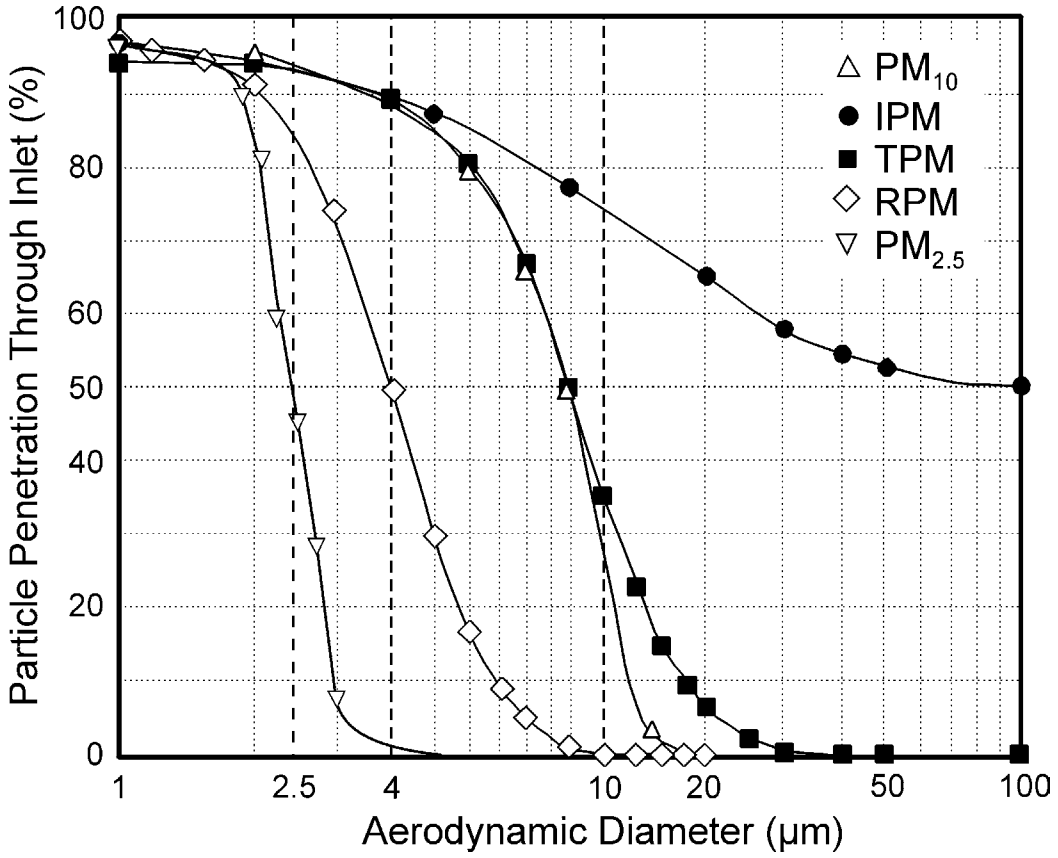

Figure 9-5. Specified particle penetration (size-cut curves) through an ideal (no-particle-loss) inlet for five different size-selective sampling criteria. Regulatory size cuts are defined in the Code of Federal Regulations; $PM_{2.5}$ (2001a), PM_{10} (2001b). $PM_{2.5}$ is also defined in the Federal 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).

Occupational Health Size Fractions. The occupational health community has defined size fractions for use in the protection of human health. This convention classifies particles into inhalable, thoracic, and respirable particles according to their upper size cuts (also shown in Figure 9-4). However, these size fractions may also be characterized in terms of their entrance into various compartments of the respiratory system. Thus, inhalable particles enter the respiratory tract, including the head airways. Thoracic particles travel past the larynx and reach

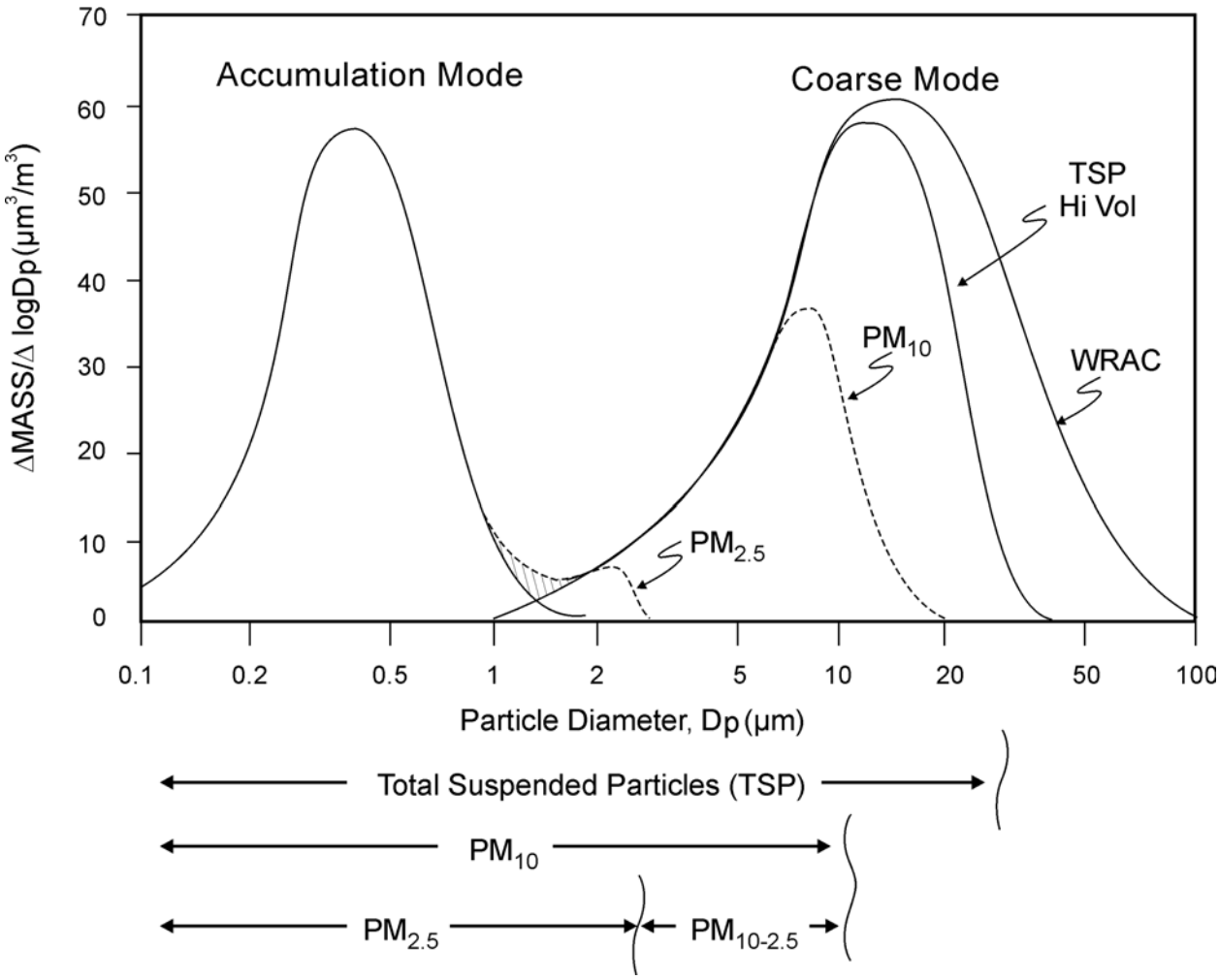

Figure 9-6. An idealized distribution of ambient particulate matter showing the accumulation mode and the coarse mode and the size fractions collected by size-selective samplers. (WRAC is the Wide Range Aerosol Classifier which collects the entire coarse mode [Lundgren and Burton, 1995].)

Source: Adapted from Wilson and Suh (1997).

the lung airways and the gas-exchange regions of the lung. Respirable particles are a subset of thoracic particles that are more likely to reach the gas-exchange region of the lung.

9.3 CHARACTERIZATION OF PM SOURCES

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 and nonroad sources. In addition to fossil fuel combustion, biomass in the form of wood is burned for fuel. Vegetation is burned to clear new land for agriculture and for building construction, to dispose of agricultural and domestic waste, to control the growth of animal or plant pests, and to manage forest resources (prescribed burning). Also shown are sources for precursor gases whose oxidation forms secondary particulate matter.

TABLE 9-1. CONSTITUENTS OF ATMOSPHERIC PARTICLES AND THEIR MAJOR SOURCES[1]

	Sources					
	Primary (PM <2.5 μm)		Primary (PM >2.5 μm)		Secondary PM Precursors (PM <2.5 μm)	
Aerosol species	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.

DRAFT-DO NOT QUOTE OR CITE

In general, the sources of fine PM are very different from those for coarse PM. Some of the mass in the fine size fraction has been formed during combustion from material that volatilized in combustion chambers and then recondensed before emission into the atmosphere. By and large, however, most ambient $PM_{2.5}$ is secondary, having been formed in the atmosphere from photochemical reactions involving precursor gases. Transport and transformations of precursors can occur over distances of hundreds of kilometers. The coarse PM constituents have shorter lifetimes in the atmosphere, so their effects tend to be more localized. Only major sources for each constituent within each broad category shown at the top of Table 9-1 are listed. Not all sources are equal in magnitude. Chemical characterizations of primary particulate emissions for a wide variety of natural and anthropogenic sources (as shown in Table 9-1) were given in Chapter 5 of the 1996 PM AQCD. Summary tables of the composition of source emissions presented in the 1996 PM AQCD and updates to that information are provided in Appendix 3D of Chapter 3 in this document. The profiles of source composition are based largely on results of various studies that collected signatures for use in source apportionment studies.

Natural sources of primary PM include windblown dust from undisturbed land, sea spray, and plant and insect debris. The oxidation of a fraction of terpenes emitted by vegetation and reduced sulfur species from anaerobic environments leads to secondary PM formation. Ammonium (NH_4^+) ions, which play a major role in regulating the pH of particles, are derived from emissions of ammonia (NH_3) gas. Source categories for NH_3 have been divided into emissions from undisturbed soils (natural) and emissions that are related to human activities (e.g., fertilized lands, domestic and farm animal waste). There is ongoing debate about characterizing emissions from wild fires (i.e., unwanted fire) as either natural or anthropogenic. Wildfires have been listed in Table 9-1 as natural in origin, but land management practices and other human actions affect the occurrence and scope of wildfires. For example, fire suppression practices allow the buildup of fire fuels and increase the susceptibility of forests to more severe and infrequent fires from whatever cause, including lightning strikes. Similarly, prescribed burning is listed as anthropogenic, but can viewed as a substitute for wildfires that would otherwise eventually occur on the same land.

The precursors to secondary PM have natural and anthropogenic sources, just as primary PM has natural and anthropogenic sources. Whereas the major atmospheric chemical

transformations leading to the formation of particulate nitrate and sulfate have been relatively well studied, those involving the formation of secondary aerosol organic carbon are still under active investigation. A large number of organic precursors are involved, many of the kinetic details still need to be determined, and many of the actual products of the oxidation of hydrocarbons have yet to be identified.

However, over the past decade, a significant amount of research has been carried out to improve the understanding of the atmospheric chemistry of secondary organic PM (SOPM) formation. Although additional sources of SOPM might still be identified, there appears to be a general consensus that biogenic compounds (monoterpenes, sesquiterpenes) and aromatic compounds (toluene, ethylbenzene) are the most significant SOPM precursors. A large number of compounds have been detected in biogenic and aromatic SOPM, although the chemical composition of these two categories has not been fully established, especially for aromatic SOPM. Transformations that occur during the aging of particles are still not adequately understood. There are still large gaps in current understanding of a number of key processes relating to the partitioning of semivolatile compounds between the gas phase and ambient particles containing organic compounds, liquid water, inorganic salts, and acids. In addition, there is a general lack of reliable analytical methods for measuring multifunctional oxygenated compounds in the gas and aerosol phases.

The relative strengths of the different sources shown in Table 9-1 can be estimated either on the basis of ambient measurements using source apportionment techniques or on the basis of chemistry-transport models using emissions inventories. For most practical purposes, the relative contributions of sources affecting different sites are determined by source apportionment models. The major approaches to source apportionment modeling have been reviewed in Section 3-3 of this document and in greater detail in Section 5-5 of the 1996 PM AQCD. These methods are capable of supplying errors in the apportionments; however, there is some subjectivity in the assignment of the input errors. The results of source-apportionment modeling studies conducted throughout the United States indicate that the combustion of fossil and biomass fuels is the major source of measured ambient $PM_{2.5}$. Fugitive dust constitutes a major fraction of $PM_{10-2.5}$ and can contribute extensively to $PM_{2.5}$, especially in arid western regions. Primary biologic particles can contribute substantially to both the $PM_{2.5}$ and $PM_{10-2.5}$ size ranges. However data for their concentrations are sparse.

Although most emphasis in this section has been placed on sources within the United States, it also should be remembered that sources outside the United States contribute to ambient PM levels that can, at times, exceed the ambient NAAQS. Dense hazes, composed mainly of dust, occur frequently during the summer in southern Florida. This dust has been emitted in the Sahara Desert and then transported across the Atlantic Ocean. Large-scale dust storms in the deserts of central Asia recently have been found to contribute to PM levels in the Northwest on an episodic basis. Not only dust but microbial pathogens and various pollutants are transported during these events. Uncontrolled biomass burning in central America and Mexico may have contributed to elevated PM levels that exceeded the daily NAAQS level for PM in Texas; and wildfires throughout the United States, Canada, Mexico, and Central America all contribute to PM background concentrations in the United States.

9.4 AMBIENT CONCENTRATIONS

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. However, as shown in Figure 9-7, 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, in the case of continuous measurement

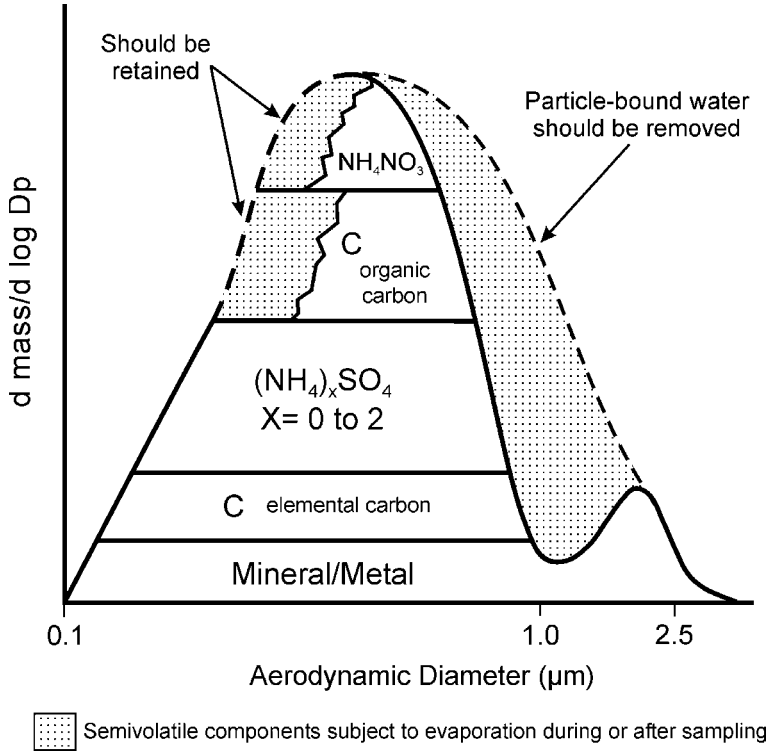

Figure 9-7. Schematic showing major nonvolatile and semivolatile components of $PM_{2.5}$. Semivolatile components are subject to partial to complete loss during equilibration or heating. The optimal technique would be to remove all particle-bound water but no ammonium nitrate or semivolatile organic PM.

techniques, particle-bound water must be reduced in situ in order to avoid measurement of large amounts of particle-bound water that would be present at higher relative humidities,. 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 need to provide new real time information to the public and the economic pressure to replace filter samplers with

continuous monitors will require a better understanding of the physics and chemistry of the semivolatile components of PM and studies of the potential health effects of these components.

9.4.2 Mass Concentrations

Data for ambient $PM_{2.5}$ and PM_{10} concentrations are obtained routinely by networks operated by various state and local agencies. Data are also collected as part of research efforts by governmental, academic and industrial groups. Data from state and local agencies are stored in the AIRS (Aerometric Information Retrieval System) data base, maintained by the U.S. Environmental Protection Agency. Concentrations of $PM_{10-2.5}$ based on FRM PM_{10} and $PM_{2.5}$ monitors are estimated by taking the difference between these two measurements. The spatial coverage and frequency of sampling depends on the resources of the agency carrying out the monitoring. Thus, the amount of data collected in a given urban area varies across the United States.

The median $PM_{2.5}$ concentration was 13 $\mu g/m^3$ in the United States on a county basis, for 1999 to 2001. The corresponding median $PM_{10-2.5}$ concentration was about 10 $\mu g/m^3$ for the same period. However, there was a good deal of variability in the annual means in different environments in the United States. The mean $PM_{2.5}$ concentration was below 7 $\mu g/m^3$ in 5% and below 17 $\mu g/m^3$ in 95% of counties that met minimum AIRS data completeness criteria for calculation of an annual mean concentration (at least 11 days data for each calendar quarter). 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 counties meeting the criteria given above. Mean $PM_{2.5}$ and $PM_{10-2.5}$ concentrations reported by the IMPROVE network were considerably lower than the lowest 5^{th} percentile values reported by state and local agencies.

9.4.3 Physical and Chemical Properties of Ambient PM

Physical and chemical properties of fine-mode and coarse-mode particles that are produced by sources listed in Table 9-1 are summarized in Table 9-2. It can readily be seen that fine and coarse particles show striking differences in the nature of their sources, their composition, and hence, their chemical properties, and in their removal processes. Differences in sources and removal processes for fine and coarse particles account for many differences in their behavior in the atmosphere. The much shorter atmospheric lifetimes of coarse particles compared to fine

TABLE 9-2. COMPARISON OF AMBIENT PARTICLES, FINE (ultrafine plus accumulation mode) AND COARSE

	Fine		Coarse
	Ultrafine	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).

particles implies that fine particles can travel much further in the atmosphere than coarse particles. The more sporadic nature of the sources of coarse particles, in addition, implies that coarse PM should be more highly spatially variable than fine PM. Elemental compositions, including trace elements by X-ray flourescence analysis, for $PM_{2.5}$ and $PM_{10-2.5}$ in two cities with

TABLE 9-3. 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	ND*	1.2	Co	0.8	ND
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	ND	Se	1.3	ND
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).

*ND = non-detectable level

different fine/coarse relationships are given in Table 9-3. The major chemical components of $PM_{2.5}$ from several sites in the U.S. Environmental Protection Agency's speciation network in the eastern, interior, and western parts of the United States are shown in Figure 9-8. Metals are not shown because their concentrations are much lower than the components shown. Concentrations of ammonium, nitrate, and sulfate ions tend to be higher at sites in the eastern and central United States compared to those in the western United States (except for the Riverside site). Concentrations of elemental and organic carbon are broadly similar across the United States (although values are highest at the Riverside site).

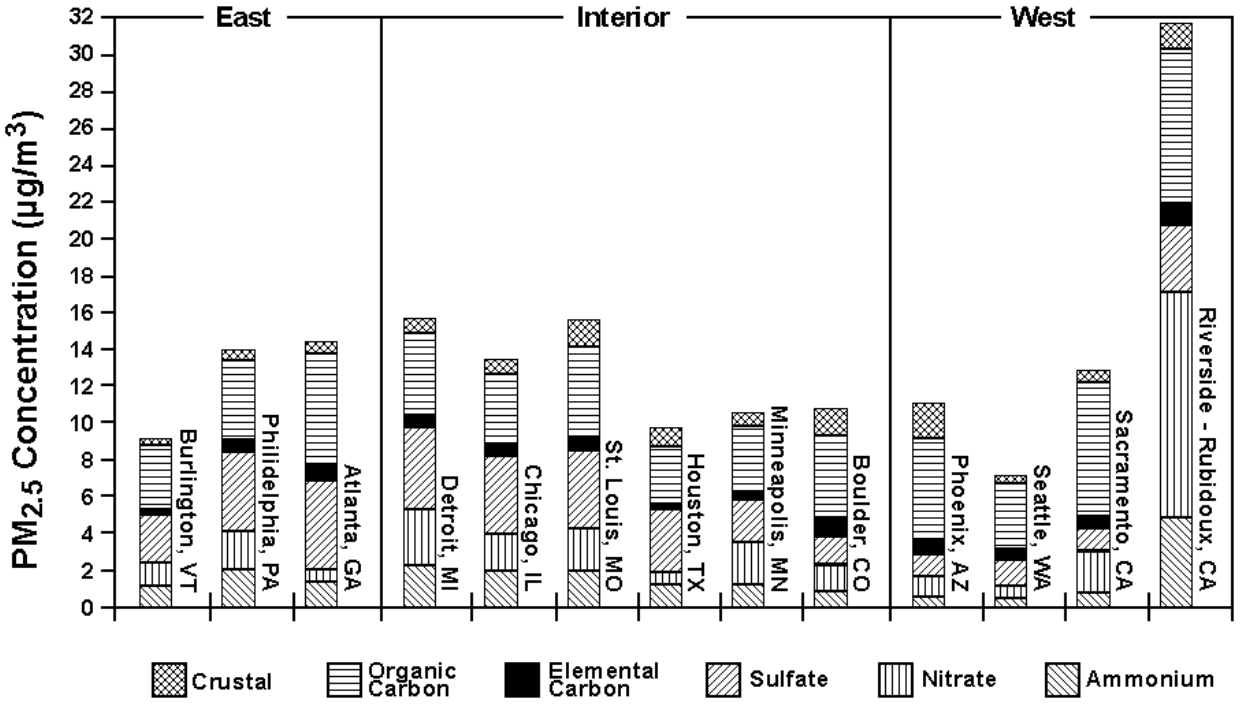

Figure 9-8. Major chemical components of $PM_{2.5}$ as determined in the U.S. Environmental Protection Agency's national speciation network from October 2001 to September 2002.

9.5 EXPOSURE TO PARTICULATE MATTER AND CO-POLLUTANTS

For airborne particulate matter (PM), an individual's total personal exposure is ideally based on measurements of the PM concentrations in the air in the individual's breathing zone as the individual moves through space and time. Total personal exposure includes exposure to ambient pollutants while outdoors, exposure while indoors to ambient pollutants that have infiltrated indoors, exposure while indoors to indoor-generated pollutants, and exposure to pollutants generated by an individual's personal activities (personal cloud) that are not recorded by outdoor or indoor monitors. Epidemiological studies frequently use ambient PM concentration as a surrogate for personal exposure to ambient PM. Therefore, an important issue for exposure analysis is determination of the quantitative relationships between concentrations of particulate matter and gaseous co-pollutants measured at stationary community air-monitoring sites (ambient pollution) and the contributions of these concentrations to personal exposures. It is useful to separate these relationships into two components: (a) the relationship between central site concentrations and outdoor concentrations; and (b) the relationship between outdoor concentrations and personal exposures to ambient PM.

9.5.1 Central Site to Outdoor Relationships

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 outdoor ambient PM concentration just outside an indoor microenvironment such as a home.

9.5.1.1 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. However, if the relationship were nonlinear, spatial variability in concentration might be more important. Chapter 3 presents analyses of spatial variability based on a substantial body of new

monitoring data from AIRS. An adequate characterization of the PM concentrations found in urban areas cannot be obtained by considering only annual average concentrations for the whole urban area. There can be considerable spatial and temporal variability in the concentration fields. Typically, annual mean concentrations are within 5 $\mu g/m^3$ of each other in urban areas metropolitan statistical areas (MSAs). The spread in values can be much greater if Consolidated MSAs (CMSAs) are considered. Even within some MSAs, concentrations measured at separate sites on individual days can differ by over 100 $\mu g/m^3$.

Pairs of sites within MSAs are correlated with each other to varying degrees, depending on the urban area. There are some very general regional patterns evident in the data base in which sites tend to be more highly correlated with each other in the eastern United States and less well correlated with each other in the western United States. Site-to-site correlations tend to be higher for a site pair where both are dominated by regional PM than for a site pair where one is more strongly influenced by local sources. Correlation coefficients are smaller for the $PM_{10-2.5}$ data than for the $PM_{2.5}$ data, indicating a higher degree of spatial variability for $PM_{10-2.5}$. However, it should be noted that at least some of this enhanced variability may be due to errors generated by the difference technique that is used to calculate $PM_{10-2.5}$ concentrations. The exceptions to very general patterns are frequent enough to prevent extrapolation from one city to another without first examining the data. Although sites may be highly correlated with each other within an MSA, this does not mean that the concentration fields are uniform, as illustrated by Figure 9-9 for three urban areas. Concentrations for the three site pairs chosen are all well correlated with each other ($r > 0.9$), but the concentrations display different degrees of uniformity. 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.

9.5.1.2 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

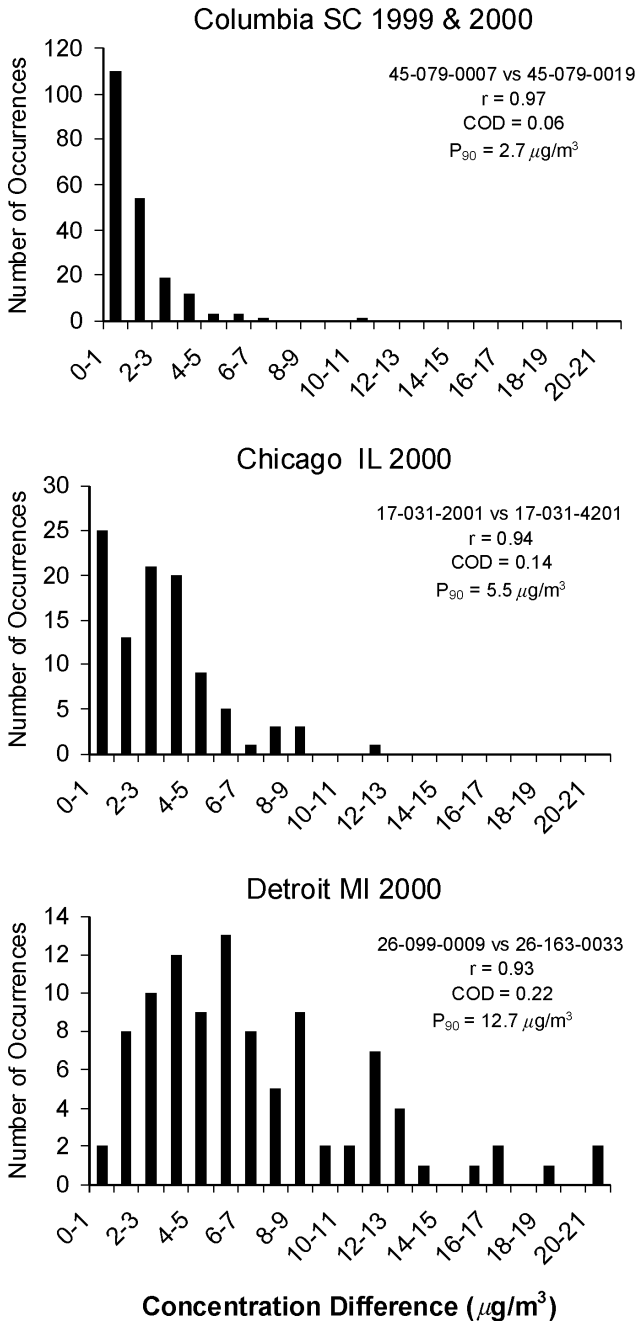

Figure 9-9. Occurrence of differences between pairs of sites in three MSAs. The absolute differences in daily average $PM_{2.5}$ concentrations between sites are shown on the x-axis and the number of occurrences on the y-axis. The MSA, years of observations, AIRS site I.D. numbers for the site pairs, 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. (2003).

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 1998, there was little information on the variations of long-term PM concentration averages within 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.

9.5.2 Home Outdoor Concentrations Versus Concentrations of Ambient PM Infiltrated Indoors

9.5.2.1 Mass Balance Model

It is 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.

$$C(AI)/C = Pa/(a+k) = F_{INF} \text{ (the infiltration factor)} \quad (9\text{-}1)$$

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,

$$A/C = y + (1\text{-}y)F_{INF} = y + (1\text{-}y)Pa/(a+k) = \alpha \text{ (the attenuation factor).} \quad (9\text{-}2)$$

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.

9.5.2.2 Separation of Total Personal Exposure into its Ambient and Nonambient Components

A person's total exposure to PM or other pollutants includes a nonambient component, usually divided into a component due to indoor-generated pollutants that are evenly distributed through out the house and a component, sometimes called the personal cloud, due to activities of the person that generate pollutants which influence that person more than other persons in the same house. Thus, total personal exposure, T, equals the sum of ambient exposure, A, and nonambient exposure, N:

$$T = A + N \tag{9-3}$$

A key variable of interest is A, the ambient exposure, i.e., the contributions of particulate matter and gaseous co-pollutants *measured at stationary outdoor air-monitoring sites* to actual personal exposures, not T, the total personal exposures due to ambient and indoor-generated pollutants. However, it is not possible to measure A or N directly. Only T and C can be measured directly. 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, [$A = C \bullet \alpha$], are important because these factors may be estimated from exposure measurements and used to estimate A, the ambient component of total personal exposure.

In recent years, the need to separate personal exposure into ambient and nonambient components has been recognized, techniques for separating total personal exposure into its ambient and nonambient components have been recommended, several papers have reported regressions which give average values of α and N, and one paper has reported individual, daily values of A and the distribution of individual, daily values of α.

Average Values

As shown in Figure 9-10, regression of individual measurements of personal exposure on the corresponding measurements of ambient concentrations yields two components of total exposure, one dependent on concentration, one not ($T = \theta_0 + \theta_1 C$). Exposure analysts associate the component independent of concentration, θ_0 , with cohort average nonambient exposure and the component dependent on concentration, θ_1, with alpha, α, the ratio of ambient exposure to

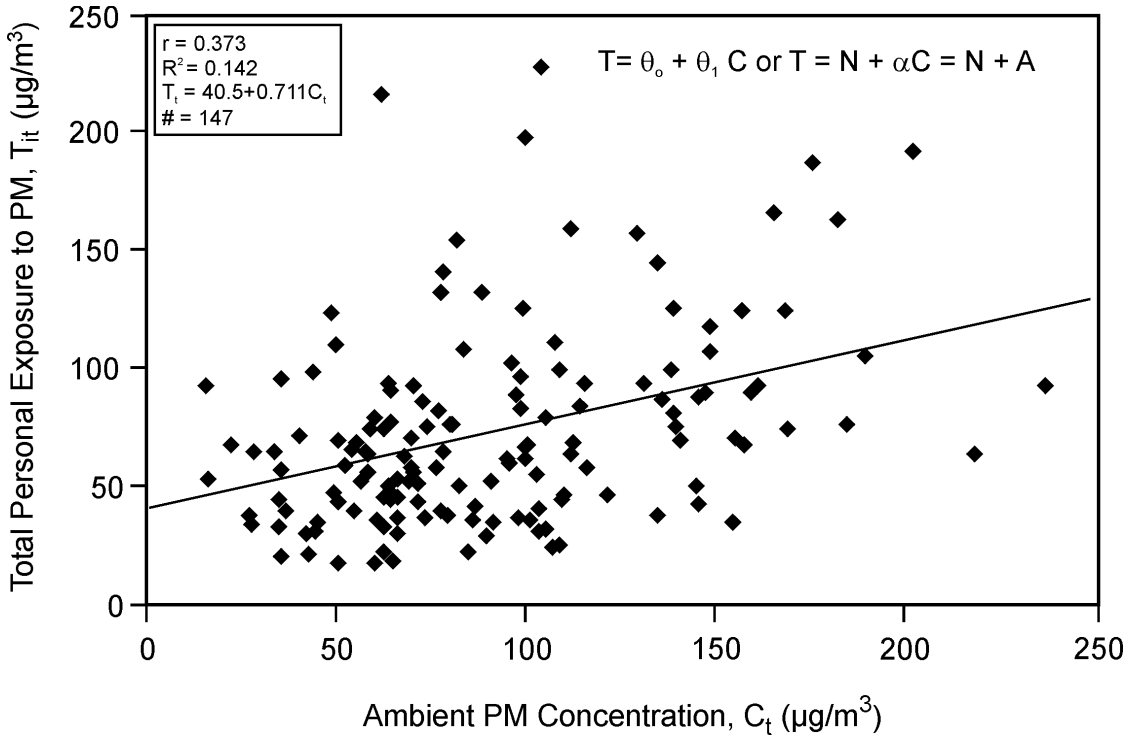

Figure 9-10. Regression analysis of daytime total personal exposures to PM_{10} versus ambient PM_{10} concentrations using data from the PTEAM study. The slope of the regression line is interpreted by exposure analysts as the average α, where $\alpha C = A$.

Source: Wilson et al. (2000)

ambient concentration ($T = N + \alpha C = N + A$; Dockery and Spengler, 1981; Ott et al., 2000; Wilson et al., 2000). Most exposure studies report the correlation between ambient concentrations and personal exposure, and many of these also report the slope of the relationship. Since the slope may be interpreted as the average alpha there are a number of studies from which estimates of the average alpha may be estimated. However, the slope may not accurately reflect the average alpha unless the data has been examined for outliers. Several studies have interpreted the slope and reported the average F_{INF} or α for cohorts (Ott et al., 2000; Wilson et al., 2000; Patterson and Eatough, 2000; Landis et al., 2001).

Individual Values

The high correlations found between ambient sulfate and personal sulfate (which has few indoor sources) suggest that a better relationship may be found between ambient concentrations and ambient exposures than between ambient concentrations and total personal exposures to PM (Ebelt et al., 2000; Sarnat et al., 2000). The PTEAM study provided sufficient information to permit estimation of individual values of ambient PM_{10} exposure, *A*. These individual values of *A* were found to be highly correlated with the corresponding ambient PM_{10} concentration, C (Figure 9-11). It is also important to determine whether or not the nonambient exposure, *N*, is a function of *C*, since if *N* is not correlated with *C, N* cannot be a confounder in a regression of health effects on ambient concentration (Zeger et al., 2000). For the PTEAM data, the correlation coefficient of *N* with *C* was r = 0.05.

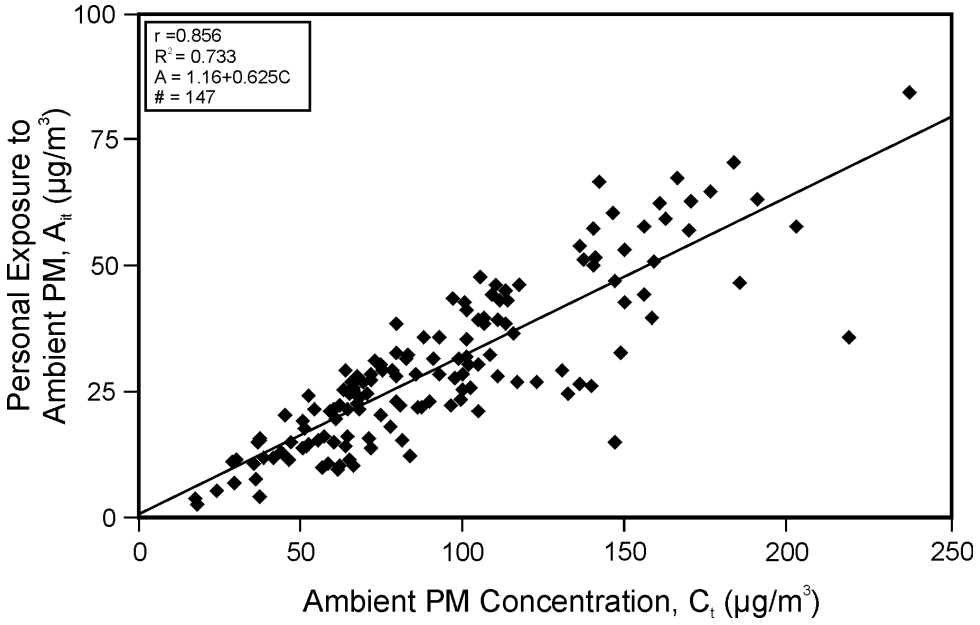

Figure 9-11. Regression analysis of daytime exposures to the ambient component of personal exposure to PM_{10} (ambient exposure) versus ambient PM_{10} concentrations.

Source: Wilson et al. (2000).

9.5.3 Variability in the Relationship Between Outdoor Concentrations and Personal Exposures

The values of the infiltration factor (F_{INF})and the attenuation factor (α) may vary from person-to-person as shown by the distribution of the infiltration factor and attenuation factor in the PTEAM study (Wilson et al., 2000). The average value of the air exchange rate, and therefore the average value of the attenuation factor may vary from season-to-season and from city-to-city due to differences in climate. The variation in average attenuation factor 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 9-12). 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 attenuation factor values 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. The attenuation factor, α, will be low for a home that is tightly closed for heating or air conditioning, but high for a home with open windows. The air exchange rate also increases as the temperature difference between indoors and outdoors increases. A temperature difference of 10 °C can almost double the air exchange rate over no indoor/outdoor temperature difference for a tight home with no windows open. Variations in wind speed, and direction appear to have a minimal influence on the air exchange rate, especially in homes with tighter construction.

Information on the infiltration rate, F_{INF} , as a function of particle size may be obtained as follows. Indoor and outdoor measurements of PM concentrations as a function of particle size are made during the night when it is assumed that there are no indoor activities occurring that might generate indoor PM. Under this assumption the indoor concentration measurement is $C(AI)$ and $C(AI)/C = F_{INF}$ (Long et al., 2000). As can be seen in Figure 9-13, F_{INF} is low for ultrafine and coarse particles but high for accumulation mode particles. F_{INF} also depends on the air exchange rate; i.e., F_{INF} increases when the air exchange rate (α) increases. The variation of the particle penetration efficiency and deposition rate as a function of particle size can also be determined by this technique (Long et al., 2000). There is little information on ambient concentration - exposure relationships for specific chemical components, except sulfate, or for specific source categories, other than what would be inferred from the size distributions.

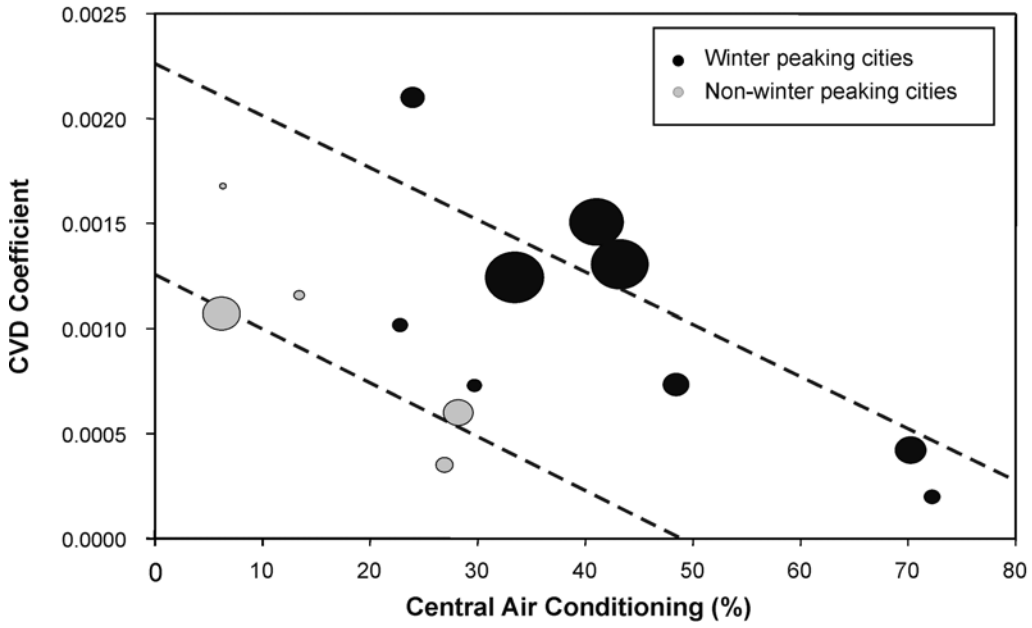

Figure 9-12. Percentage of homes with air conditioning versus the regression coefficient for the relationship of cardiovascular-related hospital admissions to ambient PM_{10} concentrations. The higher the percent air conditioning, the lower the amount of personal exposure to ambient PM per unit of ambient PM concentration, i.e., the lower attenuation factor, α, and therefore a lower regression coefficient (increase in risk per increment in PM_{10} exposure).

Source: Janssen et al. (2002).

Infiltration ratios are low for components like strong acidity (H^+) that are neutralized by indoor-generated ammonia or like ammonium nitrate (NH_4NO_3) that evaporate indoors.

9.5.4 Exposure Relations for Co-Pollutants

The key issue is whether the gaseous co-pollutants (CO, NO_2, SO_2, and O_3) likely contribute to the health effects attributed to PM or whether they are more likely to serve as surrogates for PM. To the extent that the gaseous co-pollutants may contribute to the health effects attributed to PM in a single pollutant, community time-series epidemiologic analysis, they could confound the PM associations, and the health effects attributed to PM would be overestimated. However, to the extent that the gaseous co-pollutants are more likely serving as surrogates for PM, i.e., significantly correlated with PM but not contributing to the health effects

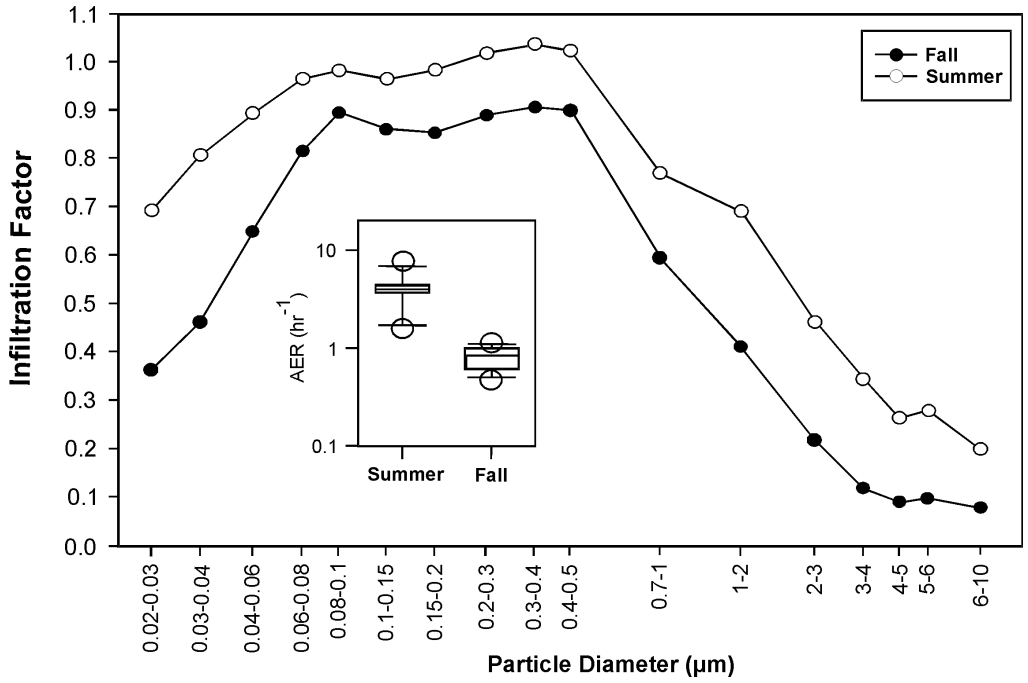

Figure 9-13. Values of geometric mean infiltration factor, F_{INF} = A/C, as a function of particle diameter for hourly nighttime data (assuming no indoor sources) for summer and fall seasons. Distribution of air exchange rates, *a*, for each season are shown in the insert.

Source: Long et al. (2000).

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, ambient gaseous co-pollutant can be potential confounders of ambient PM only if (1) both the gas and PM are able to cause the same health effects; (2) personal exposure is correlated with ambient concentrations for both particles and gases respectively; (3) the personal exposure to gases and to particles are correlated; and (4) the ambient concentrations of particles and gases are correlated. Also, the gaseous co-pollutant must not be in the formation pathway of the particles. For example, SO_2 and NO_2

are in the formation pathway for the sulfate and nitrate components of PM and O_3 is a key chemical reactant in the formation of the sulfate, nitrate, and organic compounds of PM.

Questions of particular concern from an exposure perspective include (1) How well are the daily ambient concentrations of the gaseous co-pollutants correlated with the daily ambient concentrations of PM (or specific PM components or indicators) and (2) are the daily ambient concentrations of the gaseous co-pollutants correlated with the daily personal exposures to the ambient? In order to answer these questions quantitatively, information would be needed on the spatial variability of PM indicators and the gaseous co-pollutants and on the variability of the factors which control the infiltration factors (penetration factor and deposition or removal rates).

Exposure relationships for gaseous co-pollutants were not reviewed in the exposure chapter (Chapter 5) of this document. Although there have been many exposure studies of the gaseous co-pollutants, there has been little analysis of the experimental data in terms relevant to epidemiology. Qualitative information on exposure relationships that may be inferred from the available literature is given in Table 9-4. The relationships are relative and should apply to many but not necessarily all urban areas. Before assuming a level of spatial homogeneity, it is necessary to check the representativeness of any individual site.

Based on the estimates in Table 9-4, it might be expected that the correlation between daily ambient concentrations of $PM_{2.5}$ and sulfate and personal exposure to $PM_{2.5}$ and sulfate would be high and statistically significant, but that this relationship would not be as significant for the gaseous co-pollutants. Two recent studies (Sarnat et al., 2000, 2001) provide new information relevant to possible contributions of gaseous co-pollutants to health effects attributed to PM. Personal exposure measurements were made of NO_2, O_3, and sulfate (winter and summer) and of SO_2 and EC (winter only). Ambient measurements were made of these species (same seasons) and of CO (both seasons). Personal exposures to ambient $PM_{2.5}$ were estimated by using the daily, individual ratios of personal exposure to sulfate to ambient concentrations of sulfate as an estimate of the attenuation factor for $PM_{2.5}$. Correlations among ambient concentrations, among personal exposures, and between ambient concentrations and personal exposures were examined.

Daily personal exposures to NO_2 and O_3 were not significantly correlated with daily ambient concentrations of those gaseous co-pollutants in either summer or winter. This suggests that NO_2 and O_3 are unlikely to confound the health effects associations attributed to PM in an epidemiologic analysis using daily ambient concentrations. In the winter, daily personal

TABLE 9-4. QUALITATIVE ESTIMATES OF EXPOSURE VARIABLES

	Spatial Homogeneity[1]	Infiltration Factor[2]	Stability of the Infiltration Factor[3]
Highest	$SO_4^=$, Secondary $PM_{2.5}$	CO	CO
High	$PM_{2.5}$[4]	$PM_{2.5}$, $SO_4^=$, EC[5]	$PM_{2.5}$, $SO_4^=$, EC[5]
Medium	Primary $PM_{2.5}$, $PM_{10-2.5}$, NO_2, O_3, SO_2, EC[5]	NO_2	NO_2, $PM_{10-2.5}$, UF[6]
Low	CO	$PM_{10-2.5}$	O_3, SO_2
Lowest	UF[6], trace metals	UF[6], 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. High in some cities, medium in others.
5. Elemental carbon.
6. Ultrafine particles.

Source: U.S. Environmental Protection Agency (1993, 1996b, 2000a); (Monn, 2001).

exposures to SO_2 were negatively correlated with daily ambient concentrations of SO_2. Personal exposures to CO were not reported. During summer, O_3 and NO_2 were positively and significantly associated with $PM_{2.5}$; the association with CO was positive but not significant. During winter, CO and NO_2 were positively and significantly associated with $PM_{2.5}$ while O_3 was negatively and significantly associated with $PM_{2.5}$; the association with SO_2 was negative but not significant. Similar associations of gaseous co-pollutants were found with personal exposure to $PM_{2.5}$ except that the winter association with SO_2 became significant. Also, the significant associations were more significant with personal exposure to ambient $PM_{2.5}$. This indicates that daily ambient concentrations of CO, NO_2, O_3 and SO_2 can be surrogates for daily ambient concentrations of $PM_{2.5}$ but that exposure and epidemiologic analyses including O_3 and SO_2 need to examine relationships on a seasonal basis. These studies also suggest that, for the Baltimore data set, daily ambient concentrations of $PM_{2.5}$, CO, NO_2, O_3 and SO_2 may serve as surrogates for daily personal exposures to $PM_{2.5}$ and may even be better surrogates for daily personal exposures to ambient $PM_{2.5}$. Thus, for similar urban situations, in a multiple regression using

ambient $PM_{2.5}$ concentrations and a gaseous co-pollutant, both variables would likely be surrogates for personal exposure to ambient $PM_{2.5}$.

Sarnat et al. (2001) point out that "it is inappropriate to treat one variable as a confounder of another when both variables are actually surrogates of the same thing." While the exposure results from these studies are based on a small number of non-randomly chosen subjects and therefore cannot be extrapolated with assurance to other situations, they do indicate the value of exposure analysis in identifying which of several collinear variables are likely to be causal. The work also suggests that neither NO_2, O_3, nor SO_2 are likely to confound the reported associations of ambient PM with health effects. No information was found on the correlation of ambient CO with personal exposure to CO in homes with no indoor CO sources. However, the low spatial homogeneity of ambient CO concentrations suggests that the relationship would be weak. Therefore, it seems likely, but not certain, that exposure relationships would also indicate that CO is unlikely to confound the health effects associations attributed to PM. It is important to understand that this does not indicate that these ambient pollutants do not cause health effects of the type associated with PM in epidemiologic analyses.

Sarnat et al. (2001) also suggest that some of the gaseous co-pollutants may be acting as surrogates for specific $PM_{2.5}$ source categories or components. "For subjects with COPD, ambient CO and NO_2 were not significantly associated with total personal $PM_{2.5}$, but were significantly associated with personal exposure to $PM_{2.5}$ of ambient origin and also to personal elemental carbon (EC). These significant associations may be due to the fact that motor vehicles are a major source of CO, NO_2, EC, and, to a lesser degree, to $PM_{2.5}$ of ambient origin. Conversely, ambient CO and NO_2 were not significantly associated with personal sulfate, a pollutant not associated with motor vehicle emissions. O_3, in contrast, was predominantly associated with personal sulfate (positively in summer and negatively in winter) . . ." Thus, CO, NO_2, EC, and $PM_{2.5}$ may be surrogates for personal exposure to pollutants from motor vehicles and O_3 may be a surrogate for regional sulfate. It should be noted that since $PM_{2.5}$, CO, NO_2, EC, and PM associated with motor vehicles are all correlated with each other to some extent, a community, time-series epidemiologic analysis, in one community for one time period, cannot tell whether a variable is actually responsible for relationship between concentration and health effects observed in the analysis, or whether the variable is a surrogate for the causal variable. In order to more clearly differentiate between contributor and surrogate, it will be necessary to

integrate information from toxicology and exposure analysis, as well as from epidemiologic studies in different time periods and different communities.

9.5.5 Exposure Relationships for Susceptible Subpopulations

Children, the elderly, and people with pre-existing diseases such as diabetes, respiratory disease, and cardiovascular disease appear to constitute susceptible subpopulations. A number of studies of small cohorts drawn from these and other subpopulations have been conducted recently by EPA and other organizations. Correlations between ambient concentrations and total personal exposure have been presented for a few of these. However, most of the studies have not yet been published, most of the studies have not reported the ambient exposure, and the studies have not been analyzed to determine if there are indeed exposure differences between susceptible groups and the general population.

An analysis of cohort exposure studies available in 1998 (Wallace, 2000) concluded that the personal cloud component of nonambient exposure was less for subjects with COPD than for the general population, healthy elderly subjects or children, presumably because of the higher activity level of younger or healthier subjects. However, the relationship between ambient concentrations and personal exposure for COPD patients was not better than that for other cohorts. Wallace (2000) noted that the desirable correlation is that "between personal exposure to particles originating outdoors and outdoor concentrations." However, at that time there was no information on the ambient component of personal exposure. There is still no published information that would suggest differences in exposure relationships for healthy versus susceptible populations.

9.5.6 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. 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 generated largely in the

ultrafine mode, as is the case with analogous nucleation bursts that occur at times in ambient air as the result of similar reactions with natural terpenes and other reactive hydrocarbons. Ambient and indoor generated PM also differ somewhat in their chemical composition as shown in Table 9-5.

TABLE 9-5. 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

9.6 DOSIMETRY: DEPOSITION AND FATE OF PARTICLES IN THE RESPIRATORY TRACT

Knowledge of the dose, deposition patterns, and fate 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.

9.6.1 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 both, known as oronasal breathing). However, most laboratory animals commonly used in respiratory toxicological studies are obligate nose breathers.

From the ET region, inspired air enters the TB region at the trachea. From the level of the trachea, the conducting airways then undergo branching for a number of generations. The terminal bronchiole is the most peripheral of the distal conducting airways and these lead, in humans, to the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (all of which comprise the A region). All of the conducting airways, except the trachea and portions of the mainstem bronchi, are surrounded by parenchymal tissue. This is composed primarily of the alveolated structures of the A region and associated blood and lymphatic vessels. It should be noted that the respiratory tract regions are comprised of various cell types and that there are distinct differences in the cells of airway surfaces in the ET, TB, and A regions.

Particles deposit in 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 inhaled particles to impact onto airway surfaces. The ET and upper TB airways are dominant sites of inertial impaction, a key mechanism for particles with aerodynamic diameter (D_a) >1 μm. Particles with D_a > 0.5 μm mostly are affected by sedimentation out of the airstream. Both sedimentation and inertial impaction influence deposition of particles in the same size range and occur in the ET and TB regions, with inertial impaction dominating in the upper airways and gravitational settling (sedimentation) increasingly more dominant in lower conducting airways. Particles with actual physical diameters < 1 μm are increasingly subjected to diffusive deposition due to random bombardment by air molecules, resulting in contact with airway surfaces. Particles between 0.3 and 0.5 μm in size are small enough to be little influenced by impaction or sedimentation and large enough to be minimally influenced by diffusion, and so, they undergo the least respiratory tract deposition. The interception potential of any particle depends on its physical size; fibers are of chief concern for interception, their aerodynamic size being determined mainly by their diameter. Electrostatic precipitation is deposition related to particle charge; effects of charge on deposition are inversely proportional to particle size and airflow rate. This type of deposition is likely small compared to effects of other deposition mechanisms and is generally a minor

contributor to overall particle deposition, but one recent study found it to be a significant TB region deposition mechanism for ultrafine, and some fine, particles.

Deposition of inhaled PM depends primarily on exposure concentrations, physical characteristics of the particles, lung size and structure, tidal volume, and breathing rate. Computer models have proven to be important tools to analyze PM dosimetry. The overall dosimetric model for the respiratory tract consists of several critical elements important for dose calculations including detailed descriptions of morphometry, respiratory physiology, and deposition processes. The morphometric element of the model describes the structure of the respiratory tract and its dimensions. A description of respiratory physiology provides the rates and volumes of inhaled and exhaled air which determines the amount of material that can be deposited in the respiratory tract. Deposition characterizes the initial distribution of the inhaled material within the different regions of the respiratory tract as a function of particle size. The percent deposition as a function of particle size has been calculated with the ICRP model (International Commission on Radiological Protection; ICRP, 1994) using the adult worker default respiratory parameters (see Table 6-3 in Chapter 6). Results for the total percent deposition in the respiratory tract (TOT) and the percent deposition in the ET, TB, and A regions are shown in Figure 9-14. The ET regions filters out some of the particles in the nucleation-mode size range (< 0.01 μm) and the coarse-mode size range (> 1.0 μm). Changing from nasal breathing to mouth breathing results in less deposition of particles in these size regions in the ET and more in the TB and A regions. However, there is little difference in percent deposition between nasal and mouth breathing for particles in the Ailken-mode size range (0.01 to 0.1) and the accumulation-mode size range (0.1 to 1.0). Nasal breathing removes almost all particles > 10 μm. However, mouth breathing allows some particles > 10 μm to deposit in the TB regions.

Hygroscopicity, the propensity of a material for taking up and retaining moisture, is a property of some ambient particle species and affects respiratory tract deposition. Such particles can increase in size in humid air in the respiratory tract and, when inhaled, deposit according to their hydrated size rather than their initial size. Compared to nonhygroscopic particles of the same initial size, deposition of hygroscopic aerosols in different regions varies, depending on initial size: hygroscopicity generally increases total deposition for particles with initial sizes

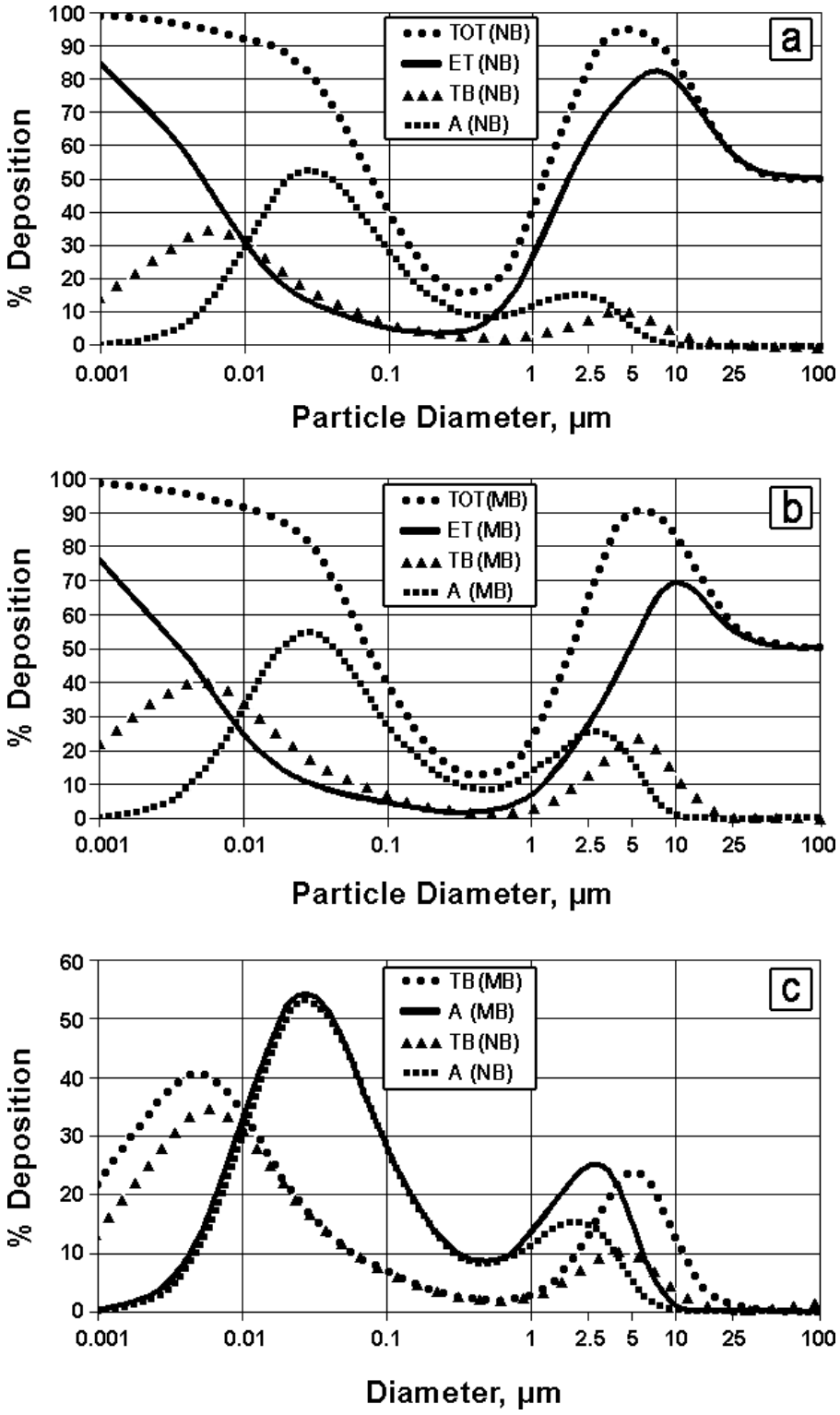

Figure 9-14. Percent deposition for total results of LUDEP model for an adult male worker (default) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions. Respiratory parameters given in Table 6-3. (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison of nasal and mouth breathing for TB and A regions.

larger than ≈0.5 μm, but decreases deposition for particles between ≈0.01 and 0.5 and again increases deposition for particles < 0.01 μm.

Enhanced particle retention occurs on carinal ridges in the trachea and throughout the segmental bronchi; and deposition "hot spots" occur at airway bifurcations or branching points. Peak deposition sites shift from distal to proximal sites as a function of particle size, with greater surface dose in conducting airways than in the A region for all particle sizes. Surface number dose (particles/cm^2/day) is much higher for fine than for coarse particles, indicating much higher numbers of fine particles depositing, with the fine fraction contributing upwards of 10,000 times greater particle number per alveolar macrophage.

Ventilation rate, gender, age, and respiratory disease status are all factors that affect total and regional respiratory tract particle deposition. In general, because of somewhat faster breathing rates and likely smaller airway size, women have somewhat greater deposition of inhaled particles than men in upper TB airways, but somewhat lower A region deposition than for men. Children appear to show four effects: (1) greater total respiratory tract deposition than adults (possibly as much as 50% greater for those < 14 years old than for adults > 14 years), (2) distinctly enhanced ET region deposition (decreasing with age from 1 year), (3) enhanced TB deposition for particles < 5 μm, and (4) enhanced A region deposition (also decreasing with age). Overall, given that children have smaller lungs and higher minute volumes relative to lung size, they likely receive greater doses of particles per lung surface area than adults for comparable ambient PM exposures. This and the propensity for young children to generally exhibit higher activity levels and associated higher breathing rates than adults likely contribute to enhanced susceptibility to ambient particle effects resulting from particle dosimetry factors. In contrast, limited available data on respiratory tract deposition across adult age groups (18 to 80 years) with normal lung function do not indicate age-dependent effects (e.g., enhanced deposition in healthy elderly adults). Altered PM deposition patterns due to respiratory disease status may put certain groups of adults (including some elderly) and children at greater risk for PM effects.

Both information noted in the 1996 PM AQCD and newly published findings discussed in this document indicate that respiratory disease status is an especially important determinant of respiratory tract particle deposition. Importantly, the pathophysiologic characteristics of chronic obstructive pulmonary disease (COPD) contribute to more heterogenous deposition patterns and

differences in regional deposition. One study indicates that people with COPD tend to breath faster and deeper than those with normal lungs (i.e., about 50% higher resting ventilation) and had about 50% greater deposition than age-matched healthy adults under typical breathing conditions, with average deposition rates 2.5 times higher under elevated ventilation rates. Enhanced deposition appears to be associated more with the chronic bronchitic than the emphysematous component of COPD. In this and other new studies, fine-particle deposition increased markedly with increased degree of airway obstruction (ranging up to 100% greater with severe COPD). With increasing airway obstruction and uneven airflow because of irregular obstruction patterns, particles tend to penetrate more into remaining better ventilated lung areas, leading to enhanced focal deposition at airway bifurcations and alveoli in those A region areas. In contrast, TB deposition increases with increasingly more severe bronchoconstrictive states, as occur with asthmatic conditions.

Differences between species in particle deposition patterns were summarized in the 1996 PM AQCD and more recently by Schlesinger et al. (1997), as discussed in Chapter 6 of this document. These differences should be considered when relating biological responses obtained in laboratory animal studies to effects in humans. Various species used in inhalation toxicology studies serving as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, A) when exposed to the same aerosol at the same inhaled concentration. This is illustrated by mathematical modeling studies that evaluate interspecies differences in respiratory tract deposition. For example, Hofmann et al. (1996) found total deposition efficiencies for all particles (0.01, 1, and 10 μm) at upper and lower airway bifurcations to be comparable for rats and humans, but when higher penetration probabilities from preceding airways in the human lung were considered, bronchial deposition fractions were mostly higher for humans. For all particle sizes, deposition at rat bronchial bifurcations was less enhanced on the carinas than in human airways. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that interspecies differences in morphologic asymmetry is a major determinant of local deposition patterns.

Models are useful for calculating percent deposition for different species. The percent deposition can then be used with exposure concentrations and respiratory parameters (tidal volume, breathing rate, lung size to calculate normalized deposition on a μg per g of lung, μg per

surface area, number of particles per alveoli or other parameters. A comparison of human and rat percent deposition, calculated using the Multiple Path Dosimetry Model (MPPD model) developed by CIIT (the Chemical Industry Institute of Technology, USA) and RIVM (Directorate-General for Environmental Protection, The Netherlands), is described by Winter-Sorkina and Cassee (2002). The percent deposition patterns and human/rat ratios will change with changes in activity levels. However, the model can be used to predict the ratios for different activity levels and to choose exposure and activity scenarios to give comparable depositions in humans and animals for extrapolation or design of experimental studies.

In a histology study, Nikula et al. (2000) examined particle retention in rats (exposed to diesel soot) and humans (exposed to coal dust). In both, the volume density of deposition increased with increasing dose. In rats, diesel exhaust particles were found mainly in lumens of the alveolar duct and alveoli, whereas in humans, retained dust was mainly in interstitial tissue. Thus, in the two species, different lung cells appear to contact retained particles and may result in different biological responses with chronic exposure.

The probability of any biological effect of PM in humans or animals depends on particle dosimetry, and subsequent particle retention, as well as underlying dose-response relationships. Interspecies dosimetric extrapolation must, therefore, consider differences in deposition, clearance, translocation, and dose-response. Even similar deposition patterns may not result in similar effects in different species, because dose also is affected by clearance mechanisms and species sensitivity. Total number of particles deposited in the lung may not be the most relevant dose metric by which to compare species; rather, the number of deposited particles per unit surface area may determine response. Even if deposition is similar in rats and humans, there would be a higher deposition density in the rat because of the smaller surface area of the rat lung. Thus, species-specific differences in deposition density are important when attempting to extrapolate health effects observed in laboratory animals to humans.

9.6.2 Particle Clearance and Translocation

Particles depositing on airway surfaces may be cleared from the respiratory tract completely or translocated to other sites within this system by regionally specific clearance mechanisms, as follow: *ET region*—mucocialiary transport, sneezing, nose wiping and blowing, and dissolution and absorption into blood; *TB region*—mucociliary transport, endocytosis by

macrophages and epithelial cells, coughing, and dissolution and absorption into blood and lymph; *A region*— macrophages, epithelial cells, interstitial, and dissolution and absorption into blood and lymph.

Regionally specific clearance defense mechanisms operate to clear deposited particles of varying particle characteristics (size, solubility, etc.) from the ET, TB, and A regions and are variously affected by different disease states. For example, particles are cleared from the ET region by mucociliary transport to the nasopharynx area, dissolution and absorption into the blood, or sneezing, wiping or blowing of the nose; but such clearance is slowed by chronic sinusitis, bronchiectasis, rhinitis, and cystic fibrosis. Also, in the TB region, poorly soluble particles are cleared mainly by upward mucociliary transport or by phagocytosis by airway macrophages that move upward on the mucociliary blanket, followed by swallowing. Soluble particles in the TB region are absorbed mostly into the blood and some by mucociliary transport. Although TB clearance is generally fast and much material is cleared in <24 h, the slow component of TB clearance (likely associated with bronchioles <1-mm diameter) results in upwards of 40 to 50% of deposited 6- to 10-μm particles being retained for >24 h and clearance half-times of about 50 days. Bronchial mucous transport is slowed by bronchial carcinoma, chronic bronchitis, asthma, and various acute respiratory infections; these are disease conditions that logically would be expected to increase retention of deposited particle material and, thereby, increase the probability of toxic effects from inhaled ambient PM components reaching the TB region. Also, spontaneous coughing, an important TB region clearance mechanism, does not appear to fully compensate for impaired mucociliary clearance in small airways and may become depressed with worsening airway disease, as seen in COPD.

Clearance of particles from the A region by alveolar macrophages and their mucociliary transport is usually rapid (< 24 h). However, penetration of uningested particles into the interstitium increases with increasing particle load and results in increased translocation to lymph nodes. Soluble particles not absorbed quickly into the blood stream and translocated to extrapulmonary organs (e.g., the heart) within minutes may also enter the lymphatic system, with lymphatic translocation probably being increased as other clearance mechanisms (e.g., removal by macrophages) are taxed or overwhelmed under "particle overload" conditions. Insoluble particles < 2 μm clear to the lymphatic system at a rate independent of size; particles of this size, more so than those > 5.0 μm, are deposited significantly in the A region. Translocation into the

lymphatic system is quite slow, and elimination from lymph nodes even slower (half-times estimated in decades). Focal accumulations of reservoirs of potentially toxic materials and their slow release for years after initial ambient PM exposure may account partially for the observation in epidemiologic studies that higher relative risks are associated with long-term ambient PM exposure than can be accounted for by additive effects of acute PM exposures. Alveolar region clearance rates are decreased in human COPD sufferers and slowed by acute respiratory infections, and the viability and functioning of alveolar macrophages are reduced in human asthmatics and in animals with viral lung infections. These observations suggest that persons with asthma or acute lung infections are likely at increased risk for ambient PM exposure effects.

Differences in regional and total clearance rates between some species reflect differences in mechanical clearance processes. The importance of interspecies clearance differences is that retention of deposited particles can differ between species and may result in differences in response to similar PM exposures. Hsieh and Yu (1998) summarize existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and human. Two clearance phases, "fast" and "slow," in the A region are associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with lymph nodes. Rats and mice are fast clearers, compared to other species. Increasing initial lung burden results in an increasing mass fraction of particles cleared by the slower phase. As lung burden increases beyond 1 mg particles/g lung, the fraction cleared by the slow phase increases to almost 100% for all species. The rate for the fast phase is similar in all species, not changing with increasing lung burden, whereas the slow phase rate decreases with increasing lung burden. At elevated burdens, the "overload" effect on clearance rate is greater in rats than in humans.

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

There are three common experimental approaches for studying the biological effects of particulate material: inhalation, instillation, and in vitro. Inhalation studies are the more realistic physiologically, and thus the most applicable to risk assessment. However, because they are expensive, time consuming and require specialized equipment and personnel, they must be supplemented by other techniques. In vitro studies using live cells are cost-effective, provide

for precise dose delivery, and permit investigators who do not have access to inhalation techniques to perform mechanistic and comparative toxicity studies of particulate material. Commonly, the initial information on likely mechanisms of action of particles is obtained through in vitro techniques. For in vitro studies, dose selection is important because it is easy to overwhelm normal defense mechanisms.

Instillation studies, in which particles suspended in a carrier such as physiological saline are applied to the airways, have certain advantages over in vitro studies. The exposed cells have normal attachments to basement membranes and adjacent cells, circulatory support, surrounding cells and normal endocrine, exocrine and neuronal relationships. Thus, instillation experiments can bridge between in vitro and inhalation studies as well as produce useful mechanistic and comparative toxicity information. Although the tracheobronchial region is most heavily dosed, alveolar regions can also be exposed via instillation techniques.

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.

Dosimetric calculations must be performed to relate tracheobronchial cell exposures from instillation in terms of particle concentrations (on a number of particles per unit surface area basis) to those occurring in human environmental exposures. Such calculations require selecting characteristics associated with the particles, the exposed subject and the environmental exposure scenario. Hence each study can present a unique dosimetric analysis. In most cases, it will be useful to know the relationship between the surface doses in instillation studies and realistic local surface doses that could occur in vivo in human subpopulations receiving the maximum potential dose. Although these subpopulations have not been completely defined some characteristics of individuals do serve to enhance the local surface deposition doses to respiratory tract cells. These characteristics include: exercise and mouth breathing non-uniform inhaled air distribution such as occurs in chronic obstructive pulmonary disease and chronic bronchitis, impaired particle clearance as occurs in some disease states and location near pollutant sources. In addition, even normal subjects exposed by inhalation are expected to have numerous sites of high local particle deposition (specifically at bifurcations) within the tracheobronchial tree.

Consideration in Chapter 6 of all these factors that could enhance local surface doses in humans led to the conclusion that an enhancement factor of 3,000 was appropriate to represent the most heavily exposed human epithelial cells. Hence, an instillation of 150 μg in a rat might be expected to represent the enhanced dose to small areas in the human TB region produced by a 24-hour exposure to 65 $\mu g/m^3$. Well-conducted instillation studies are valuable for examining the relative toxicity of particulate materials and for providing mechanistic information that is useful for interpreting in vitro and inhalation studies. However, because mechanisms of injury may vary with the delivered dose, it would be useful if instillation studies designed to provide information relevant to human risk assessment were accompanied by dosimetric calculations.

9.6.4 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 increase vapor deposition in human airways. However, these calculations do show that soluble gases are carried to higher generation airways (deeper into the lung) in the presence of particles than in the absence of particles. In addition, species such as SO_2 and formaldehyde react in water, reducing the concentration of the dissolved gas-phase species and providing a kinetic resistence to evaporation of the dissolved gas. Thus, the concentration of the dissolved species may be greater than that predicted by the equilibrium calculations. Also, certain other toxic species (e.g., nitric oxide [NO], nitrogen dioxide [NO_2], benzene, polycyclic aromatic hydrocarbons [PAH], nitro-PAH, a variety of allergens) may be absorbed onto solid particles and carried into the lungs. Thus, ambient particles may play important roles not only in inducing direct health impacts of their constituent components but also in facilitating delivery of toxic gaseous pollutants or bioagents into the lung and may, thereby, serve as key mediators of health effects caused by the overall air pollutant mix.

9.7 TOXICOLOGIC ASSESSMENT OF PARTICULATE-MATTER PROPERTIES LINKED TO HEALTH EFFECTS

Ambient PM comprises a complex mix of constituents derived from many sources, both natural and anthropogenic. Hence, the physicochemical composition of PM generally reflects the major contributing sources locally and regionally. Within this framework of source or origin, PM composition also varies significantly by the size-mode within which it is classified (ultrafine, accumulation, or coarse). It should be clear that any given particle can differ appreciably from another individual particle of similar size, but that the region of origin with all of its contributing sources determines the general composition of the generic PM in that classification mode. By its nature then, exposure to airborne ambient PM constitutes an exposure to what is very clearly a mixture of different particles of differing composition and to other gaseous co-pollutants that coexist in that air-shed.

The epidemiology information reviewed in the 1996 PM AQCD and updated in this document convincingly shows that a positive correlation exists between the levels of ambient PM pollution and mortality/morbidity. However, this correlation is based mainly on a mass metric, which is somewhat counter-intuitive considering the complexities in composition of PM and given the typically low ambient concentrations of most PM constituents, even when

fractionated by PM size. What has evolved since the 1996 PM AQCD are notable advances in our understanding that the linkages between PM exposure and health impacts appear to be most strongly related to accumulation mode particles, with combustion-derived PM typically being the most active of the source-based contributors. It is also now better appreciated that discovery of a single "magic bullet" regarding PM physicochemical attributes is not likely to occur, and perhaps the sources from which the PM derive may be the best linkage one can achieve.

Approaches to assessing likely "causation" and "biological plausibility" have attempted to integrate the wealth of epidemiologic data with the growing body of toxicology information in order to reveal coherence among the findings that support newly emerging sound hypotheses. Thus, while it is often difficult to separate the physicochemical attributes of PM that may be of health significance from the mechanisms by which individual factor(s) may function in the response, a number of hypotheses have evolved espousing various PM characteristics as potentially significant contributors to the observed health effects (reviewed by Dreher, 2000). Each of the attribute-based hypotheses has a sufficient data base to merit consideration and further investigation.

To date, toxicologic studies on PM have provided important, albeit still limited, evidence for specific PM attributes being primarily or essentially responsible for the cardiopulmonary effects linked to ambient PM. In most cases, however, exposure concentrations in laboratory studies have been inordinately high compared to the exposures at which epidemiologic studies have found effects. Reasons for this dosimetric discrepancy range from the limited numbers of animals or human subjects that can be practically studied, the uncertainty and narrow range of responsiveness of the study groups and especially the typically limited use of young, elderly, unhealthy, or otherwise at-high-risk animals or humans, especially in light of poorly understood risk factors. Thus, most of the toxicology data-base resides in the "hazard-identification" compartment of the risk assessment paradigm. However, sufficient coherence in the epidemiologic and toxicological data has provided a level of "plausibility" to the observational studies and thus opened new avenues for investigation to link PM properties and constituents to specific sources and to health outcomes. The primary PM properties thought to be related to health effects are discussed below.

9.7.1 Chemical Components and Source Categories Associated with Health Effects in Epidemiologic Studies

Epidemiologic studies using either individual chemical species or classes or using source category factors (SCF) derived from factor analysis have identified a variety of species whose ambient concentrations are statistically associated with either total mortality or more specific mortality groupings.

9.7.1.1 Toxicologically Important Components of PM

Inherent in the NRC research agenda (NRC, 1998) was the consideration that one, or perhaps a few, characteristics of PM would be associated with toxicity, and exposure monitoring could concentrate on these components. However, such narrowing of focus is not yet possible, given the wide array of PM characteristics that have been found to be associated with toxicity either through epidemiologic or toxicologic studies, as listed in Table 9-6.

TABLE 9-6. PARTICULATE MATTER ASSOCIATED WITH MORTALITY IN EPIDEMIOLOGIC STUDIES

PM Size Fractions	Ions/Elements	Carbon/Organic Fractions
Mass TSP	Sulfate ($SO_4^{=}$)	TC (Total Carbon)
Mass PM_{10}	Nitrate (NO_3^-)	EC (Elemental Carbon)
Mass-thoracic coarse PM [$PM_{10-2.5}$ or PM_{10-1}]	Transition metals (e.g., Ni)	BC (Black Carbon)
Mass-fine PM [$PM_{2.5}$ or $PM_{1.0}$]	Other toxic metals (e.g., Pb)	COH (Coefficient of Haze)
Mass-ultrafine PM [$PM_{0.1}$]	Strong Acid (H^+)	OC (Organic Carbon)
Particle number		CX (Cyclohexene-extractable Carbon)
Particle surface area		

9.7.1.2 Source Category Factors

A major goral of air pollution-health outcome studies is to relate health outcomes to specific sources of air pollutants. A number of techniques have been developed that apportion PM in ambient samples to its sources (see Section 3.3 of this document and Section 5.5 of the 1996 PM AQCD for descriptions of these techniques). These powerful techniques are limited by their ability to resolve PM produced by sources having similar compositional profiles and by the lack of data for the composition (especially the organic composition) of emissions from many sources. This limitation may be mitigated in the future by further analytical developments in analyzing the composition of PM samples. In the meantime, it is probably best to refer to source categories, although the ambiguity is removed when there are unique sources in a given area (e.g., Utah Valley steel mills). There are also three studies in which factor analysis has been used to identify several specific source category factors. In two cases (Laden et al., 2000 and Tsai et al., 2000), the source category factors (SCF) were then used in a multiple regression, the nonsignificant factors were eliminated, and the multiple regression was rerun with only the significant factors. In the third case (Mar et al., 2000), relative risk values are reported for regression with SCF one at a time but the paper states that "Regression analysis with all of the factors included in a multi-source model produced similar results." The similar results in single and multiple regressions and the low correlation between SCF indicates that there is low potential for confounding among the various SCFs.

Source categories that have been found to be significantly associated ($p < 0.05$) with total, cardiovascular, or cardiovascular plus respiratory mortality in one or more cities are shown in Table 9-7. A source category associated with motor vehicles was found in all four studies. The epidemiologic studies do not provide sufficient information to determine whether the causal factor is one or both of the gaseous co-pollutants (CO and NO_2); soot particles from cars (indexed by BS, COH, or EC); organic PM from vehicles, transition metals emitted by vehicle (Mn, Fe, Zn); or other particles generated or resuspended by vehicular traffic.

The three studies that investigated multiple source categories also found a sulfate factor. The factor reported by Laden et al. (2000) as "coal burning" contains high loadings of both selenium and sulfur and could also have been called "regional sulfate." Mar et al. (2000) refer to the factor with high sulfate specifically as "regional sulfate." They were able to make this connection because they also had a factor with a high loading of SO_2 which they called a "local

TABLE 9-7. 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

SO_2" factor. The regression with the elemental S (assumed to be sulfate) was not significant, but the regression with the regional sulfate factor was significant. This may be because the factor analysis will tend to remove other more localized sulfate sources such as $CaSO_4$ and Na_2SO_4, leaving only acid sulfates ($[NH_4]_2SO_4$, NH_4HSO_4, and H_2SO_4) for a regional sulfate factor. (In Phoenix, there was a modest loading of S in the soil factor.) Therefore, all three sulfate factors should be considered as regional sulfate.

The studies of specific chemical components and source categories are especially important because they indicate the association of health effects with the three major components of PM mass: sulfate, nitrate, and organic PM. Examination of $PM_{2.5}$ and nitrate effects, alone and in multiple regressions, indicates that $PM_{2.5}$ and nitrate were not confounded by NO_2, CO or O_3 in Santa Clara, CA (Fairley, 1999). Examination of the lag structure from the Phoenix study reveals that neither the regional sulfate factor nor the vegetative burning factor

was confounded by NO_2, CO, SO_2, or O_3. The epidemiologic results suggest the need for toxicologic studies of the sulfate, nitrate, and organic components of PM, including studies with compromised or susceptible subjects.

All of the studies that investigated multiple source categories found a soil or crustal source that was negatively associated with mortality. This suggests that the components of natural soil may have minimal toxicity unless contaminated by anthropogenic sources, such transition metals or polyaromatic hydrocarbons. In any event, the epidemiologic associations suggest additional PM components that should be investigated in toxicologic studies. Although results such as those presented above are illuminating, it should be noted that there can be ambiguity regarding the identification of source categories as the marker elements used in many of the methods used (e.g., specific rotation factor analysis) can have more than one source. As an example, before lead was phased out of gasoline it was (and still is) produced by smelters and other industries (see Appendix 3D of Chapter 3). Methods such as principal components analysis do not have optimal weighting of the factors, thereby leading to distortion in the results and although newer methods such as positive matrix factorization overcome many of these difficulties, the results are still subject to some degree of rotational ambiguity. In addition, there can be substantial spatial variability in source contributions across an urban area leading to the potential for exposure characterization error.

9.7.2 Specific Properties of Ambient PM Linked to Health Effects

9.7.2.1 Physical Properties

Fine and Thoracic Coarse Particles: In contrast to ultrafine particles, the respective roles of $PM_{2.5}$ (indicator for fine PM) and $PM_{10-2.5}$ (indicator for thoracic coarse PM) in defining health outcomes have garnered considerable research attention because they are the most frequently measured size-fractions of ambient PM and for which most health effects data exist. The fine fraction comprises most of the combustion-related constituents discussed below under chemical properties. The fine fraction has greater surface area than the thoracic coarse fraction, but much less surface area and particle number than the ultrafine fraction. To the extent that inhaled PM may carry chemicals or reactive species on their surfaces, these smaller size fractions may have an additional dimension to their toxicity (in terms of surface chemical bioavailablilty) that is not found with coarse PM. For example, acute exposure to sulfate-coated carbon black was found to

impair alveolar macrophage phagocytosis and intrapulmonary bactericidal activity in mice (Jakab et al., 1996; Clarke et al., 2000). On the other hand, coarse PM usually is of mineral (earthen) or biologic (discussed below) origin and, thus, has a less complex bioavailable chemical matrix than the finer PM mode. The relative toxicity of most earthen-derived PM has been observed to be less than that of the finer combustion-derived or surrogate ultrafine particles. However, because ambient coarse PM would tend to impact on the airways of humans, it is thought this fraction may be adverse to those with airways sensitivities or disease (e.g., asthma).

Ultrafine Particles (Size, Surface Area, Number): The physical attributes of PM - size, surface area and number - are intimately interrelated. These properties influence lung deposition, penetrance and persistence in lung tissues, and systemic transport, and, in several studies, apparently the inherent toxicity of the particle itself. While a few epidemiologic studies (Wichmann et al., 2000) show correlations between health outcomes and ultrafine (<100 nm) ambient PM, the bulk of the information regarding its toxic potential, and the role of surface area, has derived from studies of surrogate insoluble particles, such as mineral oxides (e.g., TiO_2) and carbon black (Oberdorster et al., 1994; Osier and Oberdorster, 1997; Li et al., 1997, 1999). These studies have shown that on an equivalent mass exposure-dose metric, ultrafine PM can induce more acute lung injury than fine PM. Similarly, surrogate PM with high surface areas induced more toxicity than those of like composition, but having smaller surface areas (Lison et al., 1997). On the other hand, studies have shown that composition also matters; for example MgO ultrafines produce less injury than ZnO (Kuschner et al., 1997), as did sparked carbon versus similarly generated metal oxides (Elder et al., 2000).

As with acid aerosols, studies of ultrafine particles have focused largely on effects in the lung, but inhaled ultrafine particles may also have the potential to be distributed systemically and have effects that are independent of lung effects. Recent epidemiologic studies evaluating blood viscosity as a biologic correlate of ultrafine exposures, have reported slight increases that raise the prospect of potential cardiovascular implications (Wichmann et al., 2000).

9.7.2.2 Chemical Properties

Acid Aerosols: There is relatively little new information on the effects of acid aerosols, and the basic conclusions of the the 1996 PM AQCD remain unchanged. It previously was concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects, but asthmatics may experience small decrements in pulmonary function. Long-term exposures of animals to acid aerosols, on the other hand, have been shown to alter airway morphology with epithelial cell desquamation and an increase in secretory cells, but these changes have been considered relatively minor. The conclusions about the acute health effects, however, are supported by a study by Linn and colleagues (1997), in which healthy children (and children with allergy or asthma) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 hours. While there were no significant effects on symptoms or pulmonary function when the entire group was analyzed, the allergy group did have significant acid-related increases in symptoms, although the acid concentrations were distinctly higher than typical ambient concentrations. These findings were consistent with those reported for adolescent asthmatics exposed to acid aerosols in earlier studies reported in the 1996 PM AQCD.

Although pulmonary effects of acid aerosols have been the subject of extensive research, the cardiovascular effects of acid aerosols have received little attention. One example which raises the issue is a study of acetic acid fumes where reflex mediated increases in blood pressure were found in normal and spontaneously hypertensive rats (Zhang et al., 1997). Similarly, acidic residual oil fly ash (ROFA) PM (which also contains a considerable amount of metal sulfates) was found to alter ecocardiogram (ECG) patterns in the same strain of rats at high air concentrations (Kodavanti et al., 2000). Thus, acidic components should not be entirely dismissed as possible mediators of ambient PM health effects, since so little is known about potential cardiovascular impacts or impacts in compromised subjects.

Transition Metals: The 1996 PM AQCD relied on data from occupational exposures to initially evaluate the potential toxicity of metals in PM air pollution. Since that time, in vivo and in vitro studies using ROFA or soluble transition metals have contributed substantial new information on the health effects of PM-associated soluble metals. The metals of most interest, notably the transition metals of iron, vanadium, copper, nickel, chromium, cadmium, arsenic, are ubiquitous constituents of PM-derived from anthropogenic fossil fuel emissions. Exposure

seems to be widespread with studies in autopsy specimens (1980's) showing dramatic increases in the content of the first row transition metals in lung tissues of Mexico City residents since the 1950's, consistent with industrialization and pollution (Fortoul et al., 1996). Similar studies in North America show metals in the lung tissues of urban dwellers. Although there remain uncertainties about the differential effects of one transition metal versus another, water-soluble or bioavailable metals leached from ROFA or bulk ambient PM cause a variety of biological effects. Many studies show that the action of instilled ROFA and constituent metals are pro-inflammatory (cells, mediators, and molecular signaling processes - in vivo and in vitro), and recently, they have been shown to induce cardiac arrhythmias in animal models (both healthy and diseased). In studies in which various ambient and emission source PM were instilled into rats, the soluble metal content appeared to be the primary determinant of lung injury (Costa and Dreher, 1999). However, these and the related findings on metal toxicity generally have derived from relatively high dose instillation or inhalation exposures, lending them to criticism as to their relevancy for ambient PM that is typically relatively low in metal content.

Nevertheless, a series of studies associated with the closing of a metal smelter in Utah Valley, where ambient PM extracts (containing metals and other soluble constituents) were instilled into the lungs of humans (Ghio and Devlin, 2001) and animals (Dye et al., 2001), as well as tested in vitro (Frampton et al., 1999), showed remarkable coherence with epidemiologic studies of hospitalization and mortality (Pope, 1989; Pope et al., 1999b) in the same area and at the same times of the PM samples used in the laboratory studies. The response patterns in each study paralleled the metal content. Furthermore, recent application of novel statistical approaches to the study of source-associated constituents (often metals are the elemental markers) have shown promise in linking sources with their associated emission profiles (including metals) to health outcomes in both humans (Laden et al., 2000) and animals (Clarke et al., 2000). Thus, while metals appear to be one component involved in PM associated health effects, the full story is incomplete.

Other Inorganic Constituents: The inorganic constituents of ambient PM comprise a number of compounds and elements that derive from either natural or combustion sources. The earthen or natural constituents of PM are typically silicates that contain surface and matrix

bound metals such as calcium, magnesium, aluminum, and iron. As noted above, most of these silicates do not appear to contribute much toxicity to ambient PM, as considered in this document. Sulfate and nitrate anions derived from combustion or photochemical processes usually complex with other constituents in PM - often more water-soluble ammonium ions or organic acids, as well as elemental cations, such as metals. The intrinsic, independent toxicities of sulfates (as per above) and nitrates appear to be rather low, but they may influence the toxicity or bioavailability of other PM components. Of the cations, metals represent a potential class of causal constituents for PM-associated health effects that have received considerable attention (discussed in more detail below). Sulfate, nitrate, ammonium, and metals make up a substantial part of the mass of ambient PM, often with a silicate or carbonaceous (see below) core, layering, or matrix. The majority of PM-associated metals in fine PM are derived from stationary or mobile combustion sources whereas particle sulfate, nitrate and ammonium originate from secondary atmospheric transformation reactions of involving SO_2, NO_x and biomass ammonia emissions. Organic PM has both primary and secondary sources.

Organic Constituents: Published research on the acute effects of PM-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles (DEP). Like metals, organics are common constituents of combustion-generated PM and are 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]). Although the organic fraction of PM is a poorly characterized heterogeneous mixture of a widely varying number of different compounds, strategies have been proposed for examining the health effects of potentially important organic constituents (Turpin, 1999). In contrast, the mutagenic effects of ambient PM and evidence of DNA-adducts have had more extensive study and have been linked to specific organic fractions (Binkova et al., 1999; Chorąży et al., 1994; Izzotti et al., 1996). The extent to which organic constituents of ambient PM contribute to adverse health effects identified by current epidemiology studies is not known. Nevertheless, organic constituents remain of concern regarding PM health effects due in large part to the contribution of DEP to the fine PM fraction and the health effects associated with exposure to these particles.

Diesel Exhaust Particles (DEP): There is growing toxicological evidence that DEP exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has been linked to eosinophil degranulation and induction of cytokine production suggesting that the organic constituents of DEP are responsible for the immune effects. It is known that the adjuvant-like activity of DEP is not unique, and that certain metals have analogous adjuvant effects (Lambert et al., 2000). It is important to compare the immune effects of other source-specific emissions, as well as concentrated ambient PM, to DEP to determine the extent to which exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and asthma. Other types of noncancer and carcinogenic (especially lung cancer) effects are of concern with regard to DEP exposures, as discussed in a separate EPA Health Assessment Document for Diesel Exhaust (U.S. Environmental Protection Agency, 2002).

Biological Constituents: Recent studies support the conclusion of the 1996 PM AQCD that bioaerosols (e.g., fungal spores, plant and insert fragments, airborne bacteria and viruses) at the concentrations present in the ambient environment, are unlikely to account for the health effects of ambient PM. Dose-response inhalation studies in healthy volunteers exposed to 0.55 and 50 μg endotoxin showed the threshold for pulmonary and systemic effects for endotoxin to be between 0.5 and 5.0 μg (Michel et al., 1997). Urban ambient air PM contains variable amounts of endotoxin, but the levels typically are several orders of magnitude less. The in vitro toxicological studies that have shown endotoxin associated with ambient PM to be pro-inflammatory, inducing cytokine expression in human and rat alveolar macrophages, appear to relate to the endotoxin dose to cell ratio (Becker et al., 1996; Dong et al., 1996). However, endotoxin content does appear to vary by size-mode. Monn and Becker (1999) demonstrated cytokine induction by human monocytes, characteristic of endotoxin activity, in the coarse size fraction of outdoor PM, but not in the fine fraction. Interestingly, while studies in animals models also require more endotoxin than typically found in ambient PM to induce inflammation, recent studies suggest endotoxin may have a priming effect on PM-induced inflammatory processes (Imrich et al., 1999). Thus, the role of biogenic material like endotoxin may have a subtle role that is poorly understood.

9.7.2.3 Summary

Toxicological studies have provided considerable supportive evidence that certain physicochemical particle attributes can provide elements of "causality" to observed health effects of ambient PM. A primary causative attribute may not exist but rather many attributes may contribute to a complex mechanism driven by the nature of a given PM and its contributing sources. The multiple interactions that may occur in eliciting a response in a host may make the identification of any single causal component difficult and may account for the fact that mass as the most basic metric shows the relationships to health outcomes that it does.

9.7.3 Mechanisms of Action Underlying PM Cardiovascular Effects

Numerous epidemiologic studies have shown statistically significant associations between ambient PM levels and a variety of human health endpoints, including mortality, hospital admissions, emergency department visits, respiratory illness, and symptoms measured in community surveys. These associations have been observed with both short and long-term PM exposure. There was little information available in the 1996 PM AQCD to provide biologically plausible mechanisms to support the epidemiologic observations. However, in the intervening years significant progress has been made in identifying pathophysiological effects in humans and animals exposed to various PM that can provide insight into the mechanisms by which PM may exert its effects. Potential mechanisms include neural mechanisms affecting the autonomic nervous system (ANS) via direct pulmonary reflexes or through pulmonary inflammatory processes, direct effects of PM or its components on ion channel function in myocardial cells, ischemic responses of the myocardium, or systemic responses including inflammation that can trigger endothelial cell dysfunction, and thrombosis via alterations in the coagulation cascade. The interactions between these pathways which may lead to sudden cardiac death is shown in the Figure 9-15. However, it must be noted that PM is a complex mixture of many different components and it is possible that different components may stimulate different mechanistic pathways. Thus exposure to PM may result in one or more pathways being activated, depending on the chemical and physical makeup of the PM.

There is now ample evidence that inhaled particles can affect the heart through the ANS. Direct input from the lungs to the ANS via pulmonary afferent fibers can affect both heart rate (HR) and heart rate variability (HRV). The heart is under the constant influence of both

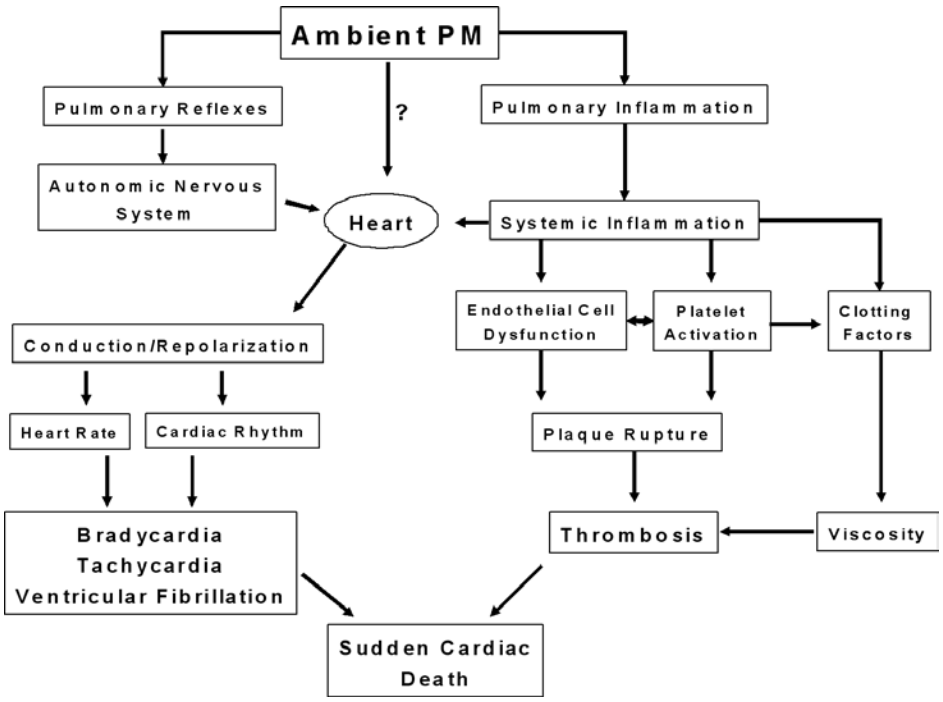

Figure 9-15. Schematic representation of potential pathophysiological pathways and mechanisms by which ambient PM may increase risk of cardiovascular morbidity and/or mortality.

sympathetic and parasympathetic innervation from the ANS; and monitoring changes in HR and HRV can provide insight into the balance between those two ANS subdivisions. During recent decades a large clinical database has developed describing a significant relationship between autonomic dysfunction and sudden cardiac death. One measure of this dysfunction, low HRV, has been implicated as a predictor of increased cardiovascular morbidity and mortality. Several independent epidemiologic panel studies of elderly volunteers (some having cardiovascular or pulmonary disease) have reported associations between PM concentrations and various measures of HR and HRV. Although there are some differences among the studies, in general they report an association between PM levels and a reduction in the standard deviation of normal to normal beat intervals (SDNN), a time-domain variable of which the reduction was associated in the Framingham Heart Study with a higher risk of death. Some studies also reported an association between PM and decreased HRV in the high frequency (HF) range, which is a reflection of parasympathetic modulation of the heart. Other studies have reported a positive association

between PM and HR; elevated HR has been associated with hypertension, coronary heart disease, and death. Thus taken as a whole, evidence from panel studies indicates that PM can directly affect the ANS in such as way as to alter heart rate and heart rate variability. However, it should be noted that lowered HRV has primarily been used as a predictor of subsequent increased mortality and morbidity. It is not clear whether a single reversible acute change in HRV places a person more at risk for an immediate adverse cardiac event. Whether changes in HRV associated with exposure to PM represent an independent risk or is just a marker of exposure is not yet known.

PM as also been shown to induce changes in conductance and repolarization of the heart as well. Repolarization duration and morphology may reflect subtle changes in myocardial substrate and vulnerability governed by changes in ion channel function. There is considerable evidence linking changes in T wave morphology, QT and T wave variability, T wave Alternans, and changes in ST segment height, to the risk of sudden death. In some studies, rodent models of susceptibility (monocrotaline injected, spontaneously hypertensive) exposed to ROFA showed exacerbated ST segment depression, a factor reflecting T wave morphology during repolarization and which as been useful in diagnosing patients with ischemic heart disease. Healthy dogs exposed to CAPS also showed changes in ST segment elevation; this was exacerbated in dogs with coronary artery occlusion.

While PM-induced changes in HRV and HR, as well as changes associated with repolarization and conductance, have the potential to progress to malignant arrhythmias, there is now evidence from both human and animal studies that PM exposure may be linked with severe events directly associated with sudden cardiac death. A recent epidemiology study of patients with implanted cardiac defibrillators reported associations between PM and increased defibrillator discharges. Presumably, some of these patients would have suffered a fatal event had they not had an implanted defibrillator. A second study reported that the risk for myocardial infarction (MI) onset increased in association with PM levels in the 2 hours preceding the MI. PM exposure has also been linked with malignant arrhythmia in some toxicology studies. Healthy rodents exposed to ROFA demonstrated an increase in serious arrhythmic events, including bradycardia. Rats treated with monocrotaline had significantly exacerbated arrhythmias, and some animals even died within 24 hours following exposure. Older rats, exposed to both ROFA and PM collected from Ottowa, also experienced increased arrhythmias.

Dogs exposed to CAPS experienced a slight bradycardia following exposure. Some of these studies involved instillation of a specific PM component (ROFA) at high concentrations, making it uncertain that these observations would hold true using ambient PM at more realistic concentrations. Nevertheless, at least one study used ambient particles collected from Ottowa, and other studies exposed animals by inhalation to CAPS. Taken as a whole, these studies provide convincing evidence that exposure of animals to high levels of PM can affect conductance and repolarization, potentially leading to fatal arrhythmias. However, it remains to be seen if these mechanisms, that can potentially explain acute mortality associated with PM exposure, operate at the lower concentrations of ambient PM to which most people are exposed.

Particulate matter could potentially affect the ANS by direct interaction with nerve ending in the lung, or indirectly through the production of inflammatory mediators. Numerous studies have documented that exposure of rodents to ROFA results in substantial lung inflammation and injury. However, due to the levels of ROFA used in many of these studies and the fact that ROFA only makes up a small portion of most airsheds, studies with ambient air particles may be more relevant. There are several studies in which humans, dogs, or rodents have been exposed to CAPS and mild pulmonary inflammation observed. Other studies have shown similar effects when ambient PM collected on filters was used. However, the level of inflammation was quite low in most of these studies, certainly lower than reported in humans or animals exposed to ozone, and it is not yet clear whether lung inflammation plays a role in PM-induced changes in the ANS.

In addition to affecting the ANS via the lung, it is also possible that PM or its components could directly attack the myocardium. There is substantial evidence that chronic exposure to fibers encountered in the workplace (e.g., asbestos) result in deposition of fibers in organs other than the lung. Some recent studies have suggested that ultrafine PM may exit the lung and deposit in other organs, including the liver and heart. So far these studies have used sources of particles not naturally found in the air (e.g., silver colloid, latex) so it is not yet clear to what extent PM actually leaves the lung or, if it does, how it interacts directly with the heart. However, there is some evidence of direct changes in the myocardium following PM exposure. For example, rats exposed to ROFA, which is made up mostly of soluble transition metals, have increased pro-inflammatory cytokine expression in the left ventricle. In another study, dogs living in highly-polluted Mexico City had histopathology changes in heart tissue compared with

dogs living in areas with low air pollution. Substantial deposits of particulate matter could be seen throughout the myocardium in the Mexico City dogs. Though preliminary, these observations point to a need for additional work to better define PM-induced changes in myocardial tissue.

Acute coronary events frequently occur as a result of thrombus formation in the site of a ruptured atherosclerotic plaque. Increased levels of clotting and coagulation factors, platelet aggregability, and blood viscosity, together with reduced fibrinolytic activity and endothelial cell dysfunction can promote a pro-coagulant state which could potentially contribute to thrombus formation. C reactive protein, a marker of systemic inflammation which correlates with some cardiac events, is positively associated with PM in several panel studies. Some of these studies also report associations between PM and enhanced blood viscosity or increased fibrinogen, a known risk factor for ischemic heart disease. Controlled human and animal exposure studies have also reported that exposure to CAPS (in humans) or ROFA (in animals) results in increased levels of blood fibrinogen. These studies suggest that PM may alter the coagulation pathways in such a way as to trigger cardiovascular events in susceptible individuals.

Panel studies have also reported associations between PM and changes in white blood cells, although these findings are not easy to interpret since some studies report positive associations while others report negative associations. Animal studies are similarly unclear, with some studies (rodents exposed to CAPS) reporting increased numbers of blood platelets and white blood cells and others (rodents exposed to ROFA) reporting decreased numbers of white blood cells. In one study, rabbits instilled with colloidal carbon had an increase in neutrophils released from the bone marrow. The same research group found an association between PM and elevated band neutrophil counts (a marker for bone marrow precursor release) in humans exposed to high levels of carbon from biomass burning during the 1997 Southeast Asian smoke-haze episodes.

Endothelial cell dysfunction may contribute to myocardial ischemia in some susceptible populations. The vascular endothelium secretes multiple factors that control vascular tone, modulate platelet activity, and influence thrombogenesis. A recent study has reported endothelial cell dysfunction in humans exposed to CAPS, as measured by dilation of the brachial artery. This vasoconstriction could be caused by an increase in circulating endothelin-1, which has been described in rats exposed to PM.

Taken as a whole, these studies are difficult to interpret but clearly indicate that PM can affect the circulatory system. However, a complete understanding of the pathways by which very small concentrations of inhaled ambient PM can produce vascular changes that can contribute to increased mortality/morbidity remains to be more fully elucidated.

9.8 HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER OBSERVED IN HUMAN POPULATION STUDIES

9.8.1 Introduction

This section assesses available scientific evidence regarding the health effects of exposure to ambient PM as observed in epidemiologic (human population) studies. The main objectives of this evaluation are (1) to summarize and evaluate strengths and limitations of available epidemiologic findings; (2) to summarize quantitative relationships between ambient PM exposures and increased human health risks; (3) to assess the biomedical coherence of findings across studied endpoints; and (4) to note the increased biologic plausibility of the available epidemiologic evidence in light of (a) linkages between specific PM components and health effects and (b) various dosimetric, mechanistic, and pathophysiologic considerations discussed earlier in this chapter.

Numerous epidemiologic studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints, including mortality, hospital admissions, emergency department visits, other medical visits, respiratory illness and symptoms measured in community surveys, and physiologic changes in pulmonary function. Associations have been consistently observed between both short- and long-term PM exposure and these endpoints. The general internal consistency of the epidemiologic database and available findings demonstrate well that notable human health effects are associated with exposures to ambient PM at concentrations currently found in many geographic locations across the United States. However, many challenges still exist with regard to delineating the magnitudes and variabilities of risk estimates for ambient PM, the ability to attribute observed health effects to specific PM constituents, the time intervals over which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations, and the nature and magnitude of the overall public health risk imposed by ambient PM exposure.

The etiology of most air pollution-related health outcomes is highly multifactorial, and the impact of ambient air pollution exposure on these outcomes is often small in comparison to that of other etiologic factors (e.g., smoking). Also, ambient PM exposure usually is accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical/chemical components. Assessment of the health effects attributable to PM and its constituents within an already-subtle total air pollution effect is therefore very challenging, even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects may not characterize fully the etiology of effects that actually depend on simultaneous exposure to multiple air pollutants. In this regard, several viewpoints existed at the time of the 1996 PM AQCD regarding how best to interpret the epidemiology data: one saw the PM exposure indicators as surrogate measures of complex ambient air pollution mixtures and the reported PM-related effects as representative of those of the overall mixture; another held that reported PM-related effects are attributable to PM components (per se) of the air pollution mixture and reflect independent PM effects; and a third viewpoint held that PM can be viewed both as a surrogate indicator, as well as a specific cause of health effects.

Several other key issues must be considered when attempting to interpret the data reviewed in this document. For example, although the epidemiology data provide strong support for the associations mentioned above, questions remain regarding potential underlying mechanisms. Even considering the progress made toward identification of anatomic sites at which particles trigger specific health effects and elucidation of biological mechanisms that underlie induction of such effects, this area of scientific inquiry is still at an early stage. Still, compared to the lack of such evidence available in the 1996 PM AQCD, there now is a stronger basis for assessing biologic plausibility of the epidemiologic observations, given notable improvement in the conceptual formulation of reasonable mechanistic hypotheses and the generation of research evidence bearing on such hypotheses. New evidence related to several hypotheses was noted in the prior section (Section 9.7) with regard to possible mechanisms by which ambient PM may exert human health effects, which tends to support the likelihood of a causal relationship between low ambient concentrations of PM and increased mortality or morbidity risks observed in human population studies. Much still remains to be done, however, to identify more confidently specific causal agents among typical ambient PM constituents.

In recent years, epidemiologic studies showing associations of ambient air pollution exposure with mortality, exacerbation of preexisting illness, and pathophysiologic changes have increased concern about the extent to which exposure to ambient air pollution exacerbates or causes harmful health outcomes at pollutant concentrations now experienced in the United States. The PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely key contributor to mortality and morbidity effects observed epidemiologically to be associated with ambient air pollution exposures. New studies appearing since the 1996 PM AQCD are important in extending earlier results to many more cities and in confirming earlier findings.

In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant health effects have been observed quite consistently, frequently being statistically significant at $p \leq 0.05$. If ambient air pollution promotes or produces harmful health effects, relatively small effect estimates from current PM concentrations in the United States and many other countries would generally be expected on biological and epidemiologic grounds. Also, magnitudes and significance levels of observed air pollution-related effects estimates would be expected to vary somewhat from place to place, if the observed epidemiologic associations denote actual effects, because (a) not only would the complex mixture of PM vary from place to place, but also (b) affected populations may differ in characteristics that could affect susceptibility to air pollution health effects. Such characteristics include sociodemographic factors, underlying health status, indoor-outdoor activities, diet, medical care access, exposure to risk factors other than ambient air pollution (such as extreme weather conditions), and variations in factors (e.g., air-conditioning) affecting human exposures to ambient-generated PM.

As noted above, small health relative risk estimates for health effects have generally been observed for ambient air pollutants, as would be expected on biological and epidemiologic grounds. In contrast to effect estimates for mortality derived for the 1952 London smog episode, i.e., relative risk (RR) exceeding 4.0 (i.e., 400% increase over baseline) for extremely high ($\geq$2 mg/m^3) ambient PM levels, effects estimates in most current epidemiology studies at distinctly lower PM concentrations (often $\leq$100 μg/m^3) are relatively small. The statistical estimates are more often subject to small (but proportionately large) differences in estimated effects of PM and other pollutants; may be sensitive to a variety of methodological choices; and

sometimes may not be statistically significant, reflecting low statistical power of the study design to detect a relatively small but real effect.

The ambient atmosphere contains numerous air pollutants, and it is important to continue to recognize that health effects associated statistically with any single pollutant may actually be mediated by multiple components of the complex ambient mix. Specific attribution of effects to any single pollutant may therefore be overly simplistic. Particulate matter is one of many air pollutants derived from combustion sources, including mobile sources. These pollutants include PM, CO, SO_2, NO_2, and O_3, all of which have been considered in various epidemiologic studies. Many volatile organic compounds (VOCs) or semivolatile compounds (SVOCs) are also emitted by combustion sources or formed in the atmosphere but have not yet been systematically considered in relation to noncancer health outcomes most usually associated with exposure to criteria air pollutants. In many newly available epidemiologic studies, harmful health outcomes are often associated with multiple combustion-related or mobile-source-related air pollutants, and some investigators have raised the possibility that PM may be a key surrogate or marker for a larger subset of the overall ambient air pollution mix. This possibility takes on added potential significance to the extent that ambient aerosols indeed may not only exert health effects directly attributable to their constituent components, per se, but also serve as carriers for more efficient delivery of water soluble toxic gases (e.g., O_3, NO_2, SO_2) deeper into lung tissue, as noted earlier in Section 9.6.4. This suggests that airborne particle effects may be enhanced by the presence of other toxic agents or mistakenly attributed to them if their respective concentrations are highly correlated temporally. Thus, although associations of PM with harmful effects continue to be observed consistently across most new studies, the newer findings do not fully resolve issues concerning relative contributions to the observed epidemiologic associations of (a) PM acting alone, (b) PM acting in combination with gaseous co-pollutants, (c) the gaseous pollutants per se, and (d) the overall ambient pollutant mix.

It is possible that, for pollutants whose ambient concentrations are not highly correlated, effects estimates in multipollutant models could be more biologically and epidemiologically sound than those in single-pollutant models, although single-pollutant models could also be credible if independent biological plausibility evidence supported designation of PM or some other single pollutant as likely being the key toxicant in the ambient pollutant mix evaluated. Because neither of these possibilities have been definitively demonstrated and there is not yet

full scientific consensus as to optimal interpretation of modeling outcomes for time series-air pollution studies, the choice of appropriate effects estimates to employ in risk assessments for ambient PM effects remains a difficult issue. Issues related to confounding by co-pollutants, along with issues related to time scales of exposure and response and concentration-response function, still apply to new epidemiologic studies relating concentrations of PM or correlated ambient air pollutants to hospital admissions, exacerbation of respiratory symptoms, asthma in children, reduced pulmonary function in children and adults, and to changes in heart rate and heart rate variability in adults. However, with considerable new experimental evidence now in hand, it is possible to hypothesize various ways in which ambient exposure to PM acting alone or in combination with other co-pollutants can plausibly be involved in the complex chain of biological events leading to harmful health effects in the human population. This newer experimental evidence, coupled with new exposure analyses results, adds much support for interpreting the epidemiologic findings discussed here as likely being indicative of causal relationships between exposures to ambient PM (or specific size or chemical components) and consequent associated increased mortality and morbidity effects.

9.8.1.2 GAM Convergence Issue

In the spring of 2002, the original investigators of a key newly available multi-city study (the National Mortality and Morbidity Air Pollution Study; NMMAPS) cosponsored by the Health Effects Institute (HEI) reported that use of the default convergence criteria setting used in the GAM routine of certain widely-used statistical software (Splus) could result in biased estimates of air pollution effects when at least two non-parametric smoothers are included in the model (Health Effects Institute letter, May 2002). The NMMAPS investigators also reported (Dominici et al., 2002), as determined through simulation, that such bias was larger when the size of the risk estimate was smaller and when the correlation between the PM and the covariates (i.e., smooth terms for temporal trend and weather) was higher. While the NMMAPS investigators reported that reanalysis (using stringent convergence criteria) of the 90 cities air pollution-mortality data did not qualitatively change their original findings (i.e., the positive association between PM_{10} and mortality; lack of confounding by gaseous pollutants; regional heterogeneity of PM, etc.), the reduction in the PM_{10} risk estimate was apparently not negligible (dropping, upon reanalysis, from ~2.1% to 1.4% excess deaths per 50 $\mu g/m^3$ increase in PM_{10}).

Issues surrounding potential bias in PM risk estimates from time-series studies using GAM analyses and default convergence criteria were raised by EPA and discussed in July 2002 at the CASAC review of the Third External Review Draft of this PM AQCD. In keeping with a follow up consultation with CASAC in August 2002, EPA encouraged investigators for a number of important published studies to reanalyze their data by using GAM with more stringent convergence criteria, as well as by using Generalized Linear Model (GLM) analyses with parametric smoothers that approximated the original GAM model. EPA, working closely with HEI, also arranged for (a) the resulting reanalyses first to be discussed at an EPA-sponsored open Workshop on GAM-Related Statistical Issues in PM Epidemiology held in November 2002; (b) then for any revamping of the preliminary analyses in light of the workshop discussions; before (c) submittal by the investigators of short communications describing the reanalyses approaches and results to EPA and HEI for peer-review by a special panel assembled by HEI; and (d) the publication of the short communications on the reanalyses, along with commentary by the HEI peer-review panel, in an HEI Special Report (2003a). Some of the short-communications included in the HEI Special Report (2003) included discussion of reanalyses of data from more than one original publication because the same data were used to examine different issues of PM-mortality associations (e.g., concentration/response function, harvesting, etc.). In total, reanalyses were reported for more than 35 originally published studies.

9.8.1.3 Ambient PM Increments Used to Report Risk Estimates

The effect of mortality from exposure to PM or other pollutants is usually expressed in this document as a relative risk or risk rate (RR) relative to a baseline mortality or morbidity rate. The pollutant concentration increments utilized here to report Relative Risks (RR's) or Odds Ratio for various health effects are as follow for short-term ($\leq$ 24 h) exposure studies: 50 $\mu g/m^3$ for PM_{10}; 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$; 155 nmoles/m^3 (15 $\mu g/m^3$) for SO_4^{-2}; and 75 nmoles/m^3 (3.6 $\mu g/m^3$, if as H_2SO_4) for H^+. The increments for short-term studies are the same as were used in the 1996 PM AQCD, a choice now driven by more current data. In the 1996 PM AQCD, the same increments were used for the long- and short-term exposure studies. However, for long-term exposure studies, 20 $\mu g/m^3$ is the increment used here for PM_{10} and

10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. These latter increments, derived from new 1999-2001 data, are smaller than those used in the 1996 PM AQCD for long-term exposure studies.

9.8.2 Short-Term Particulate Matter Exposure Effects on Mortality

This section focuses primarily on discussion of short-term PM exposure effects on mortality, but also highlights some morbidity effects in relation to the mortality findings. Morbidity effects of short-term ambient PM exposures are discussed more fully in subsection (9.8.3). Subsequent sections include discussion of mortality and morbidity effects of long-term PM exposures.

Summary of Previous Findings on Short-Term Particulate Matter Exposure-Mortality Effects

Time-series mortality studies reviewed in the 1996 PM AQCD provided strong evidence that ambient PM air pollution is associated with increased daily mortality. The 1996 PM AQCD summarized about 35 PM-mortality time series studies published between 1988 and 1996. The available information from those studies was consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. The PM_{10} relative risk estimates derived from the PM_{10} studies reviewed in the 1996 PM AQCD suggested that an increase of 50 μg/m^3 in the 24-h average of PM_{10} is associated with an increased risk of premature total mortality (total deaths minus accidents and injuries) mainly on the order of RR = 1.025 to 1.05 (i.e., 2.5 to 5.0% excess risk) in the general population, with statistically significant increases being reported more broadly across the range of 1.5 to 8.5% per 50 μg/m^3 PM_{10}. Higher relative risks were indicated for the elderly and for those with preexisting respiratory conditions. Also, based on the then recently published Schwartz et al. (1996) analysis of Harvard Six City data, the 1996 PM AQCD found the RR for excess total mortality in relation to 24-h fine-particle concentrations to be in the range of RR = 1.026 to 1.055 per 25 μg/m^3 $PM_{2.5}$ (i.e., 2.6 to 5.5% excess risk per 25 μg/m^3 $PM_{2.5}$). Relative risk estimates for morbidity and mortality effects associated with standard increments in ambient PM_{10} concentrations and for fine-particle indicators (e.g., $PM_{2.5}$, sulfates, etc.) were presented in Chapters 12 and 13 of the 1996 PM AQCD (see Appendix 9A); and those effect estimates are updated below in light of the extensive newly available evidence discussed in Chapter 8 of this document.

Although numerous studies reported PM-mortality associations, several important issues needed to be addressed in interpreting those relative risks. The 1996 PM AQCD extensively discussed the following critical issues: (1) seasonal confounding and effect modification, (2) confounding by weather, (3) confounding by co-pollutants, (4) measurement error, (5) functional form and threshold, (6) harvesting and life shortening; and (7) the roles of specific PM components.

Season-specific analyses are often not feasible because of small magnitudes of expected effect size or small sample sizes (low power) available for some studies. Some earlier studies had suggested possible season-specific variations in PM coefficients, but it was not clear if these were caused by peak variations in PM effects from season to season, varying extent of PM correlations with other co-pollutants, or weather factors during different seasons. The likelihood of PM effects being accounted for mainly by weather factors was addressed by various methods that controlled for weather variables in most studies (including some involving sophisticated synoptic weather pattern evaluations); and that possibility was found to be very unlikely.

Many early PM studies considered at least one co-pollutant in the mortality regression, and an increasing number have examined multiple pollutants. At times, when PM indices were significant in single-pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate PM associations. In multiple-pollutant models performed by season, the PM coefficients became less stable, again possibly because of varying correlations of PM with co-pollutants among seasonal or smaller sample sizes. However, in many studies, PM indices showed the highest significance in both single- and multiple-pollutant models. Thus, PM-mortality associations did not appear to be seriously distorted by co-pollutants.

Interpretation of the relative significance of each pollutant in mortality regression in relation to its relative causal strength was difficult, however, because of lack of quantitative information on pertinent exposure measurement errors among the air pollutants. Measurement errors can influence the size and significance of air pollution coefficients in time series regression analyses, an issue also important in assessing confounding among multiple pollutants, because the varying extent of such errors among pollutants may influence corresponding relative significance. The 1996 PM AQCD discussed several types of exposure measurement and characterization errors, including site-to-site variability and site-to-person variability. These

errors are thought to bias the estimated PM coefficients downward in most cases, but there was insufficient quantitative information available at the time to allow estimation of such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Some studies indicated that associations were seen at levels even below then-existing PM standards. It was considered difficult, however, to statistically evaluate the possibility of a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, use of relative risk (rate ratio) derived from log-linear Poisson models was deemed adequate.

The extent of prematurity of death, i.e., mortality displacement (or harvesting) in observed PM-mortality associations has important public health policy implications. At the time of the 1996 PM AQCD review, only a few studies had investigated this issue. Although one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalized because this estimate was obtained for identifiable PM episodes. Insufficient evidence then existed to suggest the extent of prematurity for nonepisodic periods, from which most of the recent PM relative risks were derived.

Only a few PM-mortality studies had analyzed fine particles and chemically specific components of PM. Using Harvard Six Cities Study data, Schwartz et al. (1996) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+). The results suggested that $PM_{2.5}$ was associated most significantly with mortality among the PM components. Although H^+ was not significantly associated with mortality in this and earlier analyses, the smaller sample size for H^+ than for other PM components made direct comparison difficult. Also, certain respiratory morbidity studies showed associations between hospital admissions and visits with components of PM in the fine-particle range. Thus, the 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play an especially important role in observed PM mortality effects.

Overall, then, the outcome of assessment of the above key issues in the 1996 PM AQCD can be thusly summarized: (1) observed PM effects are not likely seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) observed PM effects are not likely significantly confounded by weather; (3) observed PM effects may be confounded or modified to some extent by co-pollutants, and such extent may vary from season to season; (4) determining

the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement/characterization error among pollutants (there was not sufficient information on this); (5) no clear evidence for any threshold for PM-mortality associations was reported (statistically identifying a threshold from existing data also was considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was conducted to investigate harvesting in nonepisodic U.S. data); and (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in light of historical data, biological plausibility, and results from morbidity studies, a greater role for fine particles than coarse particles was suggested as being likely.

Updated Epidemiologic Findings for Short-Term Ambient Particulate Matter Exposure Effects on Mortality

With regard to updating the assessment of PM effects in light of new epidemiologic information published since the 1996 PM AQCD, the most salient key points on relationships between short-term PM exposure and mortality (drawn from Chapter 8 discussions in this document) can be summarized as follows.

Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality analyses, several of which investigated multiple cities using consistent data analytical approaches. With only a few exceptions, the estimated mortality RR's in these studies are generally positive, many are statistically significant, and they generally comport well with previously reported PM-mortality effects estimates delineated in the 1996 PM AQCD. There are also now numerous additional studies demonstrating associations between short-term (24-h) PM exposures and various morbidity endpoints.

Several new studies conducted time series analyses in multiple cities. The major advantage of these studies over meta-analyses for multiple "independent" studies is the consistency in data handling and model specifications, thus eliminating variation in results attributable to study design. Also, many of the cities included in these studies were ones for which no earlier time series analyses had been conducted. Therefore, unlike regular meta-analysis, they likely do not suffer from omission of negative studies caused by publication bias. Furthermore, any spatial or geographic variability of air pollution effects can be systematically evaluated in such multi-city analyses.

PM_{10} Effect Size Estimates

Table 9-8 provides a summary of effect size estimates per variable 24-h PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ increments for total and cause-specific (cardiovascular; respiratory) mortality derived from epidemiological studies of U.S. and Canadian cities. These include GAM results mainly derived from newly published studies and/or their reanalyses using stringent convergence criteria (GAM strict) or other acceptable alternate methods (e.g., GLM). Also included in the table are results for some key studies assessed in the 1996 PM AQCD that did not use GAM (default) analyses. Emphasis is placed in Table 9-8 (and ensuing analogous tables) on the presentation of percent excess risk increases per designated increment in a given PM indicator (e.g., PM_{10}, $PM_{2.5}$, etc.), as derived from single-pollutant PM models of the type indicated.

The NMMAPS (Samet et al., 2000a,b) analysis of the 90 largest U.S. cities using default GAM convergence criteria found a combined nationwide RR estimate of ~2.3% increase in total mortality per 50-$\mu g/m^3$ increase in PM_{10}. The NMMAPS effect size estimates did vary somewhat by U.S. region, with the largest estimate being for the Northeast (4.5% for a 1-day lag, the lag typically showing maximum effect size for most U.S. regions). Reanalyses of the same NMMAPS data reported by Dominici et al. (2002; 2003), using other more appropriate alternative analyses, found smaller effect size estimates, the overall nationwide combined estimate being ~1.4% excess total deaths per 50 $\mu g/m^3$ PM_{10} increment based on GAM analyses with stringent convergence criteria (the effect size of the Northeast region being about twice the nationwide estimate). Reanalyses for various other U.S. multi-city studies, as well as single-city analyses, obtained PM_{10} effect sizes mainly in the range of 2.5 to 5.0% per 50-$\mu g/m^3$ increase in PM_{10}. There is some evidence that, if the effects over multiple days are considered, the effect size may be larger. What heterogeneity existed for the estimated PM_{10} risks across NMMAPS cities could not be explained with the city-specific explanatory variables (e.g., as the mean levels of pollution and weather), mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error.

Original results reported for the multi-city APHEA study showed generally consistent associations between mortality and both SO_2 and PM indices in western European cities, but not for central and eastern European cities. More recent studies from APHEA II analyses, however, found analogous increased risks to be associated with PM exposures in central and eastern Europe as in western European cities; and these findings were substantiated by reanalyses

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8. ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 µg/m^3 PM_{10} Increase	% increase (95% CI) per 25 µg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 µg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
MORTALITY: Total (nonaccidental) Mortality					
Ito and Thurston (1996) Chicago, IL	GAM not used	2.47 (1.26, 3.69)	—	—	PM_{10} 38 (max 128)
Styer et al. (1995) Chicago, IL	GAM not used	4.08 (0.08, 8.24)	—	—	PM_{10} 37 (4, 365)
Kinney et al. (1995) Los Angeles, CA	GAM not used	2.47 (−0.17, 5.18)	—	—	PM_{10} 58 (15, 177)
Pope et al. (1992) Utah Valley, UT	GAM not used	7.63 (4.41, 10.95)	—	—	PM_{10} 47 (11, 297)
Schwartz (1993) Birmingham, AL	GAM not used	5.36 (1.16, 9.73)	—	—	PM_{10} 48 (21, 80)
Schwartz et al. (1996) Schwartz (2003a) Boston, MA	GAM Strict GLM NS GLM BS GML PS		5.3 (3.5, 7.1) 5.7 (3.7, 7.6) 5.0 (3.1, 7.0) 4.5 (2.5, 6.5)	 0.7 (−1.9, 3.4)	PM_{10} 24.5 (SD 12.8) $PM_{2.5}$ 15.7 (SD 9.2) $PM_{10-2.5}$ 8.8 (SD 7.0)
Schwartz et al. (1996) Schwartz (2003a) Knoxville, TN	GAM Strict GLM NS GLM BS GLM PS		3.1 (0.0, 6.2) 3.0 (−0.3, 6.6) 2.8 (−0.5, 6.3) 2.6 (−0.8, 6.1)	 1.7 (−2.7, 6.3)	PM_{10} 32.0 (SD 14.5) $PM_{2.5}$ 20.8 (SD 9.6) $PM_{10-2.5}$ 11.2 (SD 7.4)
Schwartz et al. (1996) Schwartz (2003a) St. Louis, MO	GAM Strict GLM NS GLM BS GLM PS		2.6 (0.9, 4.3) 2.4 (0.6, 4.1) 2.6 (0.9, 4.4) 2.3 (0.6, 4.1)	 0.3 (−2.1, 2.7)	PM_{10} 30.6 (SD 16.2) $PM_{2.5}$ 18.7 (SD 10.5) $PM_{10-2.5}$ 11.9 (SD 8.5)
Schwartz et al. (1996) Schwartz (2003a) Steubenville, OH	GAM Strict GLM NS GLM BS GLM PS		2.4 (−0.4, 5.3) 1.7 (−1.3 4.8) 1.5 (−1.5, 4.6) 1.8 (−1.2, 4.9)	 5.2 (0.0, 10.7)	PM_{10} 45.6 (SD 32.3) $PM_{2.5}$ 29.6 (SD 21.9) $PM_{10-2.5}$ 16.1 (SD 13.0)
Schwartz et al. (1996) Schwartz (2003a) Portage, WI	GAM Strict GLM NS GLM BS GLM PS		2.6 (−1.2, 6.6) 0.8 (−3.3, 5.1) 1.5 (−2.7, 5.8) 1.1 (−3.1, 5.4)	 0.7 (−4.0, 5.6)	PM_{10} 17.8 (SD 11.7) $PM_{2.5}$ 11.2 (SD 7.8) $PM_{10-2.5}$ 6.6 (SD 6.8)

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m³ PM_{10} Increase	% increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
MORTALITY: Total (nonaccidental) Mortality (cont'd)					
Schwartz et al. (1996) Schwartz (2003a) Topeka, KS	GAM Strict GLM NS GLM BS GLM PS		1.6 (−5.3, 9.0) 2.7 (−5.0, 10.9) 1.3 (−6.2, 9.3) 1.4 (−6.3, 9.6)	 −3.0 (−8.1, 2.3)	PM_{10} 26.7 (SD 16.1) $PM_{2.5}$ 12.2 (SD 7.4) $PM_{10-2.5}$ 14.5 (SD 12.2)
Schwartz et al. (1996) Schwartz (2003a) 6 Cities, Overall	GAM Strict GLM NS GLM BS GLM PS		3.5 (2.5, 4.5) 3.3 (2.2, 4.3) 3.0 (2.0, 4.0) 2.9 (1.8, 4.0)		PM_{10} means 17.8-45.6 $PM_{2.5}$ means 11.2-29.6 $PM_{10-2.5}$ means 6.6-16.1
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis-St. Louis	GAM Strict GLM NS	2.0 (0.0, 4.1) 1.0 (-1.5, 3.6)	2.0 (0.5, 3.5) 1.3 (-0.5, 3.0)	0.0 (-2.2, 2.3) -0.5 (-3.0, 2.0)	PM_{10} 30.6 (SD 16.2) $PM_{2.5}$ 18.7 (SD 10.5) $PM_{10-2.5}$ 11.9 (SD 8.5)
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis-Steubenville	GAM Strict GLM NS	2.5 (−1.7, 7.0) 1.5 (−1.7, 4.9)	1.5 (−1.6, 4.7) 0.5 (−2.7, 3.8)	4.6 (−0.7, 10.1) 4.0 (−1.6, 10.0)	PM_{10} 45.6 (SD 32.3) $PM_{2.5}$ 29.6 (SD 21.9) $PM_{10-2.5}$ 16.1 (SD 13.0)
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis-Topeka	GAM Strict GLM NS	−3.5 (−11.6, 5.4) −5.4 (−14.3, 4.4)	1.5 (−6.5, 10.2) −0.5 (−9.5, 9.4)	−3.7 (−9.2, 2.1) −4.7 (−10..8, 1.8)	PM_{10} 26.7 (SD 16.1) $PM_{2.5}$ 12.2 (SD 7.4) $PM_{10-2.5}$ 14.5 (SD 12.2)
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis - Knoxville	GAM Strict GLM NS	6.1 (1.5, 11.0) 5.1 (−0.2, 10.7)	4.3 (0.9, 7.8) 3.8 (−0.1, 7.8)	3.5 (−1.0, 8.2) 3.0 (−1.9, 8.2)	PM_{10} 32.0 (SD 14.5) $PM_{2.5}$ 20.8 (SD 9.6) $PM_{10-2.5}$ 11.2 (SD 7.4)
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis - Boston	GAM Strict GLM NS	6.1 (3.6, 8.8) 5.6 (2.8, 8.5)	5.1 (3.3, 6.9) 4.0 (1.9, 6.2)	1.3 (−1.1, 3.7) 1.8 (−1.0, 4.6)	PM_{10} 24.5 (SD 12.8) $PM_{2.5}$ 15.7 (SD 9.2) $PM_{10-2.5}$ 8.8 (SD 7.0)
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis - Madison	GAM Strict GLM NS	1.0 (−4.6, 7.0) −1.5 (−7.7, 5.1)	1.5 (−2.7, 5.9) −1.2 (−5.7, 3.5)	0.0 (−4.8, 5.0) −1.0 (−6.2, 4.5)	PM_{10} 17.8 (SD 11.7) $PM_{2.5}$ 11.2 (SD 7.8) $PM_{10-2.5}$ 6.6 (SD 6.8)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m³ PM_{10} Increase	% increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
MORTALITY: Total (nonaccidental) Mortality (cont'd)					
Klemm et al. (2000) Klemm and Mason (2003) Six City reanalysis - overall	GAM Strict GLM NS	3.5 (2.0, 5.1) 2.5 (0.8, 4.3)	3.0 (2.0, 4.1) 2.0 (0.9, 3.2)	0.8 (−0.6, 2.1) 0.5(−1.0, 2.0)	PM_{10} means 17.8-45.6 $PM_{2.5}$ means 11.2-29.6 $PM_{10-2.5}$ means 6.6-16.1
Samet et al. (2000a,b) Dominici et al. (2002, 2003) 90 Largest U.S. Cities	GAM strict GLM NS	1.4 (0.9, 1.9) 1.1 (0.5, 1.7)	—	—	PM_{10} mean range 15.3-52.0
Schwartz (2000a) Schwartz (2003b) 10 U.S. cities	GAM Strict GLM NS	3.4 (2.6, 4.1) 2.8 (2.0, 3.6)	—	—	PM_{10} mean range 27.1-40.6
Burnett et al. (2000) Burnett and Goldberg (2003) 8 Canadian Cities	GAM Strict GLM NS (6 knots/yr)	3.2 (1.1, 5.5) 2.7 (−0.1, 5.5)	2.8 (1.2, 4.4) 2.1 (0.1, 4.2)	1.9 (−0.1, 3.9) 1.8 (−0.6, 4.4)	PM_{10} 25.9 (max 121) $PM_{2.5}$ 13.3 (max 86) $PM_{10-2.5}$ 12.9 (max 99)
Chock et al. (2000) Pittsburgh, PA	GAM not used		< 75 years 2.6 (2.0, 7.3) > 75 years 1.5 (−3.0, 6.3)	< 75 years 0.7 (−1.7, 3.7) > 75 years 1.3 (−1.3, 3.8)	NR
Clyde et al. (2000) Phoenix, AZ	GAM not used	6 (> 0, 11)	—	—	PM_{10} mean 45.4
Fairley (1999) Fairley (2003) Santa Clara County, CA	GAM Strict GLM NS	7.8 (2.8, 13.1) 8.3 (2.9, 13.9)	8.1 (1.6, 15.0) 7.0 (1.4, 13.0)	4.5 (−7.6, 18.1) 3.3 (−5.3, 12.6)	PM_{10} 34 (6, 165) $PM_{2.5}$ 13 (2, 105) $PM_{10-2.5}$ 11 (0, 45)
Gamble (1998) Dallas, TX	GAM not used	−3.56 (−12.73, 6.58)	—	—	PM_{10} 24.5 (11, 86)
Goldberg et al. (2000) Goldberg and Burnett (2003) Montreal, CAN	GAM Strict GLM NS	—	4.2 ($p < 0.05$) 1.5 ($p > 0.05$)	—	$PM_{2.5}$ 17.6 (4.6, 71.7)
Klemm and Mason (2000) Atlanta, GA	GAM not used	—	4.8 (−3.2, 13.4)	1.4 (−11.3, 15.9)	$PM_{2.5}$ 19.9 (1.0, 54.8) $PM_{10-2.5}$ 10.1 (0.2, 39.5)
Levy (1998) King Co., WA	GAM not used	7.2 (−6.3, 22.8)	1.76 (−3.53, 7.34)	—	PM_{10} 29.8 (6.0, 123.0) PM_1 28.7 (16.3, 92.2)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
MORTALITY: Total (nonaccidental) Mortality (cont'd)					
Lipfert et al. (2000a) Philadelphia, PA	GAM not used	5.99 (p > 0.055)	4.21 (p < 0.055)	5.07 (p > 0.055)	PM_{10} 32.20 (7.0, 95.0) $PM_{2.5}$ 17.28 (−0.6, 72.6) $PM_{10-2.5}$ 6.80 (−20.0, 28.3)
Lippmann et al. (2000) Ito (2003) Detroit, MI	GAM Strict GLM NS	3.3 (−2.0, 8.9) 3.1 (−2.2, 8.7)	1.9 (−1.8, 5.7) 2.0 (−1.7, 5.8)	3.2 (−1.9, 8.6) 2.8 (−2.2, 8.1)	PM_{10} 31 (12, 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50) mean (5%, 95%)
Moolgavkar (2000a) Moolgavkar (2003) Los Angeles, CA	GAM Strict GLM NS	2.4 (0.5, 4.2) 2.3 (0.5, 4.1)	1.5 (0, 3.0) 1.4 (−0.4, 3.2)	—	PM_{10} median 44 (7, 166) $PM_{2.5}$ 22 (4, 86)
Moolgavkar (2000a) Moolgavkar (2003) Cook Co., IL	GAM Strict GLM NS	2.4 (1.4, 3.5) 2.6 (1.6, 3.6)	—	—	PM_{10} median 35 (3, 365)
Ostro (1995) San Bernadino and Riverside Counties, CA	GAM not used	—	0.28 (−0.61, 1.17)	—	$PM_{2.5}$ 32.5 (9.3, 190.1) (estimated from visibility)
Schwartz (2000b) Schwartz (2003a) Boston, MA	GLM NS	—	5.8 (4.5, 73) (15-day) 9.7 (8.2, 11.2) (60-day)	—	$PM_{2.5}$ 15.6 (±9.2)
Laden et al. (2000) Schwartz (2003a) Six City source-oriented analysis	GLM PS	—	−5.1 (−13.9, 4.6) crustal 9.3 (4.0, 14.9) traffic 2.0 (−0.3, 4.4) coal	—	$PM_{2.5}$ same as Six City
Tsai et al. (2000) Newark, NJ	GAM not used	5.65 (4.62, 6.70)	4.34 (2.82, 5.89)	—	PM_{15} 55 (SD 6.5) $PM_{2.5}$ 42.1 (SD 22.0)
Tsai et al. (2000) Camden, NJ	GAM not used	11.07 (0.70, 22.51)	5.65 (0.11, 11.51)	—	PM_{15} 47.0 (SD 20.9) $PM_{2.5}$ 39.9 (SD 18.0)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m³ PM_{10} Increase	% increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
MORTALITY: Total (nonaccidental) Mortality (cont'd)					
Tsai et al. (2000) Elizabeth, NJ	GAM not used	−4.88 (−17.88, 10.19)	1.77 (−5.44, 9.53)	—	PM_{15} 47.5 (SD 18.8) $PM_{2.5}$ 37.1 (SD 19.8)
Cardiorespiratory Mortality:					
Tsai et al. (2000) Newark, NJ	GAM not used	7.79 (3.65, 12.10)	5.13 (3.09, 7.21)	—	PM_{15} 55 (SD 6.5) $PM_{2.5}$ 42.1 (SD 22.0)
Tsai et al. (2000) Camden, NJ	GAM not used	15.03 (4.29, 26.87)	6.18 (0.61, 12.06)	—	PM_{15} 47.0 (SD 20.9) $PM_{2.5}$ 39.9 (SD 18.0)
Tsai et al. (2000) Elizabeth, NJ	GAM not used	3.05 (-11.04, 19.36)	2.28 (-4.97, 10.07)	—	PM_{15} 47.5 (SD 18.8) $PM_{2.5}$ 37.1 (SD 19.8)
Total Cardiovascular Mortality					
Ito and Thurston (1996) Chicago, IL	GAM not used	1.49 (-0.72, 3.74)	—	—	PM_{10} 38 (max 128)
Pope et al. (1992) Utah Valley, UT	GAM not used	9.36 (1.91, 17.36)	—	—	PM_{10} 47 (11, 297)
Fairley (1999) Fairley (2003) Santa Clara County, CA	GAM Strict GLM NS	8.5 (0.6, 17.0) 8.9 (1.3, 17.0)	6.3 (−4.1. 17.9) 6.7 (−2.5, 16.7)	(GAM strict) 5.0 (−13.3,27.3)	PM_{10} 34 (6, 165) $PM_{2.5}$ 13 (2, 105) $PM_{10-2.5}$ 11 (0, 45)
Goldberg et al. (2000) Goldberg and Burnett (2003) Montreal, CAN	GAM Strict GLM NS	—	3.48 (−0.16, 7.26)	—	$PM_{2.5}$ 17.6 (4.6, 71.7)
Lipfert et al. (2000a) Philadelphia, PA (7-county area)	GAM not used	6.92 ($p < 0.055$)	10.26 ($p < 0.055$)	7.57 ($p > 0.055$)	PM_{10} 32.20 (7.0, 95.0) $PM_{2.5}$ 17.28 (−0.6, 72.6) $PM_{10-2.5}$ 6.80 (−20.0, 28.3)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Total Cardiovascular Mortality (cont'd)					
Lippmann et al. (2000) Ito (2003) Detroit, MI	GAM Strict GLM NS	5.4 (−2.6, 14.0) 4.9 (−3.0, 13.5)	2.2 (−3.2, 7.9) 2.0 (−3.4, 7.7)	6.7 (−1.0, 15.0) 6.0 (−1.6, 14.3)	PM_{10} 31 (12, 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50) mean (10%, 90%)
Mar et al. (2000) Mar et al. (2003) Phoenix, AZ	GAM Strict GLM NS	9.7 (1.7, 18.3) 9.5 (0.6, 19.3)	18.0 (4.9, 32.6) 19.1 (3.9, 36.4)	6.4 (1.3, 11.7) 6.2 (0.8, 12.0)	18.0 (4.9, 32.6) 19.1 (3.9, 36.4)
Moolgavkar (2000a) Moolgavkar (2003) Los Angeles, CA	GAM Strict GLM NS	4.5 (1.6, 7.5) 3.9 (0.6, 7.4)	2.6 (0.4, 4.9) 1.7 (−0.8, 4.3)	—	PM_{10} median 44 (7, 166) $PM_{2.5}$ median 22 (4, 86)
Moolgavkar (2000a) Moolgavkar (2003) Cook Co., IL	GAM Strict GLM NS	2.2 (0.3, 4.1) 1.2 (−0.8, 3.1)	—	—	PM_{10} median 35 (3, 365)
Ostro et al. (2000) Ostro et al. (2003) Coachella Valley, CA	GAM Strict GLM NS	5.5 (1.6, 9.5) 5.1 (1.2, 9.1)	9.8 (−5.7, 27.9) 10.2 (−5.3, 28.3)	2.9 (0.7, 5.2) 2.7 (0.4, 5.1)	PM_{10} 47.4 (3, 417) $PM_{2.5}$ 16.8 (5, 48) $PM_{10-2.5}$ 17.9 (0, 149)
Ostro (1995) San Bernadino and Riverside Counties, CA	GAM not used	—	0.69 (−0.34, 1.74)	—	$PM_{2.5}$ 32.5 (9.3, 190.1) (estimated from visibility)
Total Respiratory Mortality:					
Ito and Thurston (1996) Chicago, IL	GAM not used	6.77 (1.97, 11.79)	—	—	PM_{10} 38 (max 128)
Pope et al. (1992) Utah Valley, UT	GAM not used	19.78 (3.51, 38.61)	—	—	PM_{10} 47 (11, 297)
Fairley (1999) Fairley (2003) Santa Clara County, CA	GAM Strict GLM NS	10.7 (−3.7, 27.2) 10.8 (−3.4, 27.1)	11.7 (−9.8, 38.3) 13.5 (−3.6, 33.7)	(GAM strict) 32.1 (−9.1, 92.2)	PM_{10} 34 (6, 165) $PM_{2.5}$ 13 (2, 105) $PM_{10-2.5}$ 11 (0, 45)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-8 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$ AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Total Respiratory Mortality (cont'd)					
Goldberg et al. (2000) Goldberg and Burnett (2003) Montreal, CAN	GAM Strict GLM NS	—	21.6 (13.0, 31.0)	—	$PM_{2.5}$ 17.6 (4.6, 71.7)
Lippmann et al. (2000) Ito (2003) Detroit, MI	GAM Strict GLM NS	7.5 (−10.5, 29.2) 7.9 (−10.2, 29.7)	2.3 (−10.4, 16.7) 3.1 (−9.7, 17.7)	7.0 (−9.5, 26.5) 6.4 (−10.0, 25.7)	PM_{10} 31 (12, 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50) mean (10%, 90%)
Ostro (1995) San Bernadino and Riverside Counties, CA	GAM not used	—	2.08 (−0.35, 4.51)	—	$PM_{2.5}$ 32.5 (9.3, 190.1) (estimated from visibility)
COPD Mortality:					
Moolgavkar (2000a) Moolgavkar (2003) Cook Co., IL	GAM Strict GLM NS	5.5 (0.2, 11.0) 4.5 (−1.6, 11.0)	—	—	PM_{10} median 35 (3, 365)
Moolgavkar (2000a) Mookgavkar (2003) Los Angeles, CA	GAM Strict GLM NS	4.4 (−3.2, 12.6) 6.2 (−3.4, 16.7)	1.0 (−5.1, 7.4) 0.5 (−6.8, 8.4)	—	PM_{10} median 44 (7, 166) $PM_{2.5}$ 22 (4, 86)

* Both original published studies and recent reanalyses reported in HEI (2003) Special Report for many cited here. Original studies published before 1996 and Schwartz et al. (1996) were assessed in 1996 PM AQCD.

** Where GAM not used in original analysis cited, original results are reported here. Otherwise reanalyses results are reported here if GAM (default) was used in original analysis. GAM strict = GAM with stringent criteria; GLM = general linear model; NS = natural splines; BS = B splines; PS = penalized splines.

*** Mean (minimum, maximum) 24-h PM level in parentheses unless otherwise noted.

DRAFT-DO NOT QUOTE OR CITE

reported in HEI (2003). The pooled estimate of PM_{10}-mortality relative risks for European cities comport well with estimates derived from U.S. data.

Certain other individual-city studies using similar methodology in analyses for each city (but not generating combined overall pooled effect estimates) also report variations in PM effect size estimates between cities and in their robustness to inclusion of gaseous co-pollutants in multi-pollutant models. Thus, one cannot entirely rule out that real differences may exist in excess risk levels associated with varying size distributions, number, or mass of the chemical constituents of ambient PM; the combined influences of varying co-pollutants present in the ambient air pollution mix from location to location or season to season; or to variations in the relationship between exposure and ambient PM concentration.

Nevertheless, there still appears to be reasonably good consistency among the results derived from reanalyses (HEI, 2003) of several new multi-city studies providing pooled analyses of data combined across multiple cities (thought to yield the most precise effect size estimates). Such reanalyses produced an overall U.S. nationwide effects estimate for percent excess total (nonaccidental) deaths per 50 $\mu g/m^3$ increase in 24-h PM_{10} of 1.4% at 1 day lag (1.1% using GLM) in the 90 largest U.S. cities (about twice that in the Northeast region); 3.4% using GAM (2.8% GLM) for average of 0 and 1 day lags in 10 U.S. cities; 3.6% using GAM (2.7% GLM) for 1-day lag in the eight largest Canadian cities; and 3.0% using GAM (2.1% GLM) in APHEA2 for average of and 1-day lags for 29 European cities during 1990-1997. These combined estimates are reasonably consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD (i.e., 1.5 to 8.5% per 50 $\mu g/m^3$ PM_{10}). These and other excess risk estimates from many other individual-city studies comport well with a number of new studies confirming increased cause-specific cardiovascular- and respiratory-related mortality, and those noted below as showing ambient PM associations with increased cardiovascular and respiratory hospital admissions and medical visits.

Fine and Coarse Particle Effect Size Estimates. Table 9-6 also summarizes effects estimates (RR values) for increased mortality and/or morbidity associated with variable increments in short-term (24-h) exposures to PM_{10}, ambient fine particles indexed by various fine PM indicators ($PM_{2.5}$, sulfates, H^+, etc.) and for inhalable thoracic fraction coarse particles (i.e., $PM_{10-2.5}$) in U.S. and Canadian cities. The table includes studies that were highlighted in

comparable tables in the 1996 PM AQCD which did not use GAM analyses with default convergence criteria; or for those few that did and have since been reanalyzed by more appropriate alternative methods, the results of the reanalyses are presented as reported in HEI (2003). For purposes of comparison across studies, results of single-pollutant models are presented in these tables; co-pollutant model results were summarized and/or discussed in more detail in Chapter 8 Appendix tables and/or main text.

The effect size estimates derived for $PM_{2.5}$ as an ambient fine particle indicator (especially those based on directly measured versus estimated $PM_{2.5}$ levels) generally appear to fall in the range of 2.0 to 6.0% increase in total (nonaccidental) deaths per 25-$\mu g/m^3$ increment in 24-h $PM_{2.5}$ for U.S. and Canadian cities. Cause-specific effects estimates appear to fall mainly in the range of 2.0 to 10.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for cardiovascular or combined cardiorespiratory mortality (although one estimate for cardiovascular mortality ranged up to about 19%) and 2.0 to 14.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for respiratory mortality in U.S. cities.

As noted earlier, there was only one study in the 1996 PM AQCD, the Harvard Six Cities study (Schwartz et al., 1996), in which the relative importance of fine and coarse particles was examined. That study suggested that fine particles, but not coarse particles, were associated with daily mortality. Both Schwartz (2003a) and Klemm and Mason (2003) have carried out reanalyses of the same Harvard Six-Cities data set using GAM (stringent convergence criteria) and/or other alternate approaches and have essentially replicated the original findings, abeit finding slightly smaller effect size estimates than obtained in the original GAM (default) analyses reported by Schwartz et al. (1996). In addition, several more studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality (see Figure 9-16). Although some of these studies (e.g., the Santa Clara County, CA, analysis and the eight largest Canadian cities analysis) suggest that $PM_{2.5}$ is more important than $PM_{10-2.5}$ in predicting mortality fluctuations, several others (e.g., the Phoenix, AZ, and Santiago, Chile studies) seem to suggest that $PM_{10-2.5}$ may be as important as $PM_{2.5}$ in certain locations (some shown to date being drier, more arid areas). Seasonal dependence of PM components' associations observed in some of the locations (e.g., higher coarse [$PM_{10-2.5}$] fraction estimates for summer than winter in Santiago, Chile) hint at possible contributions of biogenic materials (e.g., molds, endotoxins, etc.) to the observed coarse particle effects in at least some locations. Overall, for U.S. and Canadian cities, effect size estimates for the coarse fraction ($PM_{10-2.5}$) generally appear to fall mainly in the range of

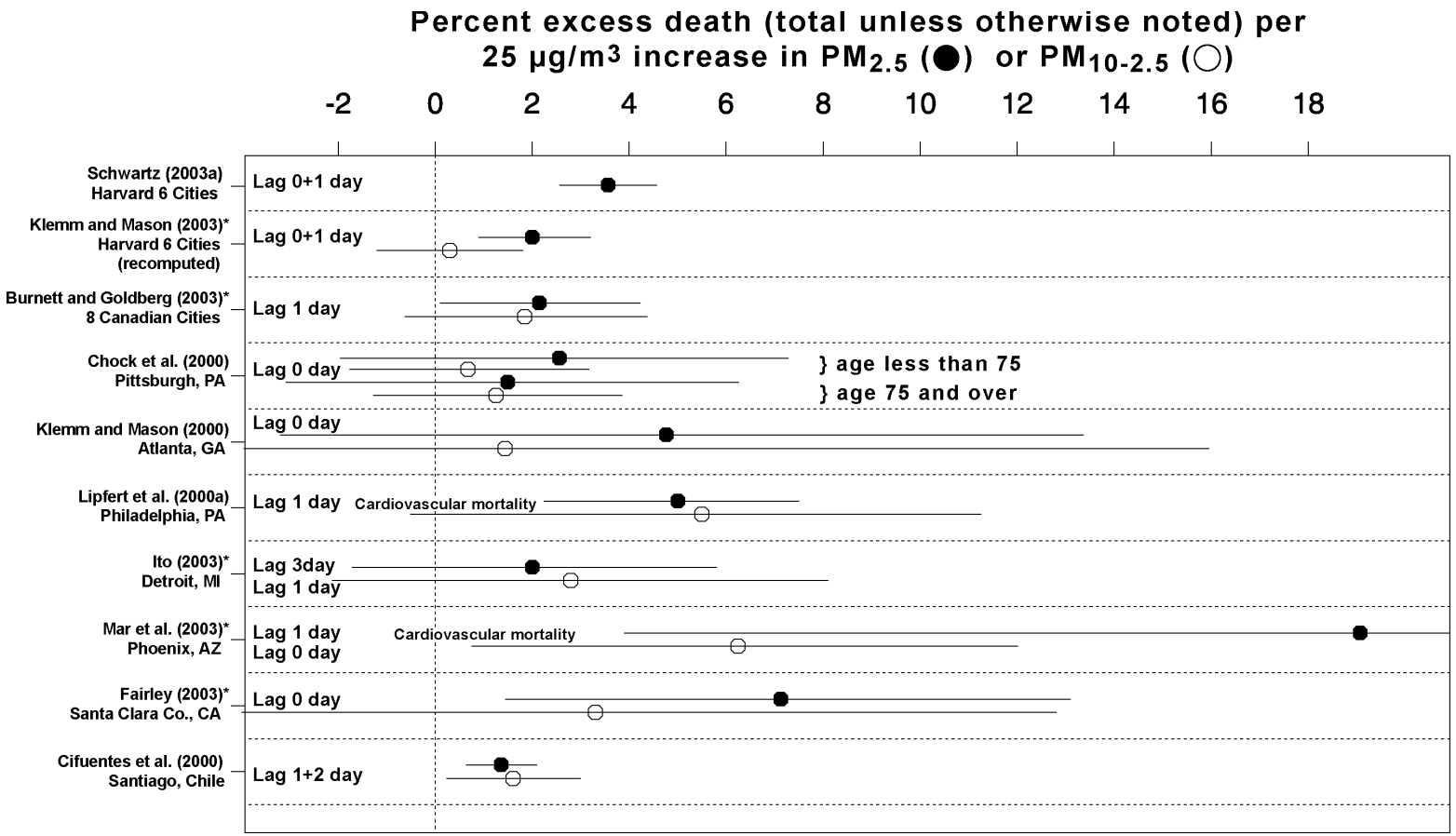

Figure 9-16. Percent excess risks estimated per 25-µg/m^3 increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10-2.5}$ data for multiple years. All lags = 1 day, unless indicated otherwise.

DRAFT-DO NOT QUOTE OR CITE

2.0 to 6.0% excess total (nonaccidental) deaths per 25 $\mu g/m^3$ of 24-h $PM_{10-2.5}$. Respective increases for cause-specific mortality mainly range from ~3.0 to 7.0% for cardiovascular and from ~3.0 to 6.0% for respiratory causes per 25-$\mu g/m^3$ increase in 24-h $PM_{10-2.5}$.

Chemical Components of Particulate Matter. Several new studies examined the role of specific chemical components of PM in relation to mortality risks. Studies of U.S. and Canadian cities showed mortality associations with one or more of several specific fine particle components of PM, including H^+, sulfate, nitrate, as well as COH; but their relative importance varied from city to city, likely depending, in part, on their concentrations (e.g., no clear associations in those cities where H^+ and sulfate levels were very low [i.e., circa nondetection limits]). Figure 9-17 depicts relatively consistent estimates of total mortality excess risk resulting from a 5-$\mu g/m^3$ increase in sulfate, possibly reflecting impacts of sulfate per se or perhaps sulfate serving as a surrogate for fine particles in general. Sulfate effect size estimates generally fall in the range of 0.5 to 4% excess total mortality per 5-$\mu g/m^3$ increase for U.S. and Canadian cities.

A significant factor in some western cities is the occasional occurrence of high levels of windblown crustal particles that constitute much of the coarse PM fraction. The small-size tail of windblown crustal particles extends into the $PM_{2.5-1}$ (intermodal) size range at times constituting a substantial fraction of $PM_{2.5}$. Claiborn et al. (2000) report that in Spokane, WA, $PM_{2.5}$ constitutes about 30% of PM_{10} on dust event days, but 48% on days preceding the dust event. The intermodal fraction represents about 51% of $PM_{2.5}$ during windblown dust events, about 28% on preceding days. However, PM_1 in Spokane often shows little change during dust events, when coarse particles (presumably crustal particles) are transported into the region. The lack of increased mortality during time periods with high wind speeds and presumably high crustal material concentrations was shown by Schwartz et al. (1999) for Spokane, and by Pope et al. (1999a) for three cities in the Wasatch front region of Utah. Other recent studies suggest that coarse particles, as well as fine particles, may be associated with excess mortality in certain U.S. locations e.g., in Phoenix, AZ (Smith et al., 2000; Clyde et al., 2000; Mar et al., 2000) the Coachella Valley of California (Ostro et al., 2000), Mexico City (Castillejos et al., 2000) or Santiago, Chile (Cifuentes et al., 2000). However, the coarse particle association with mortality does not appear to be caused by the crustal components. An important advantage of using

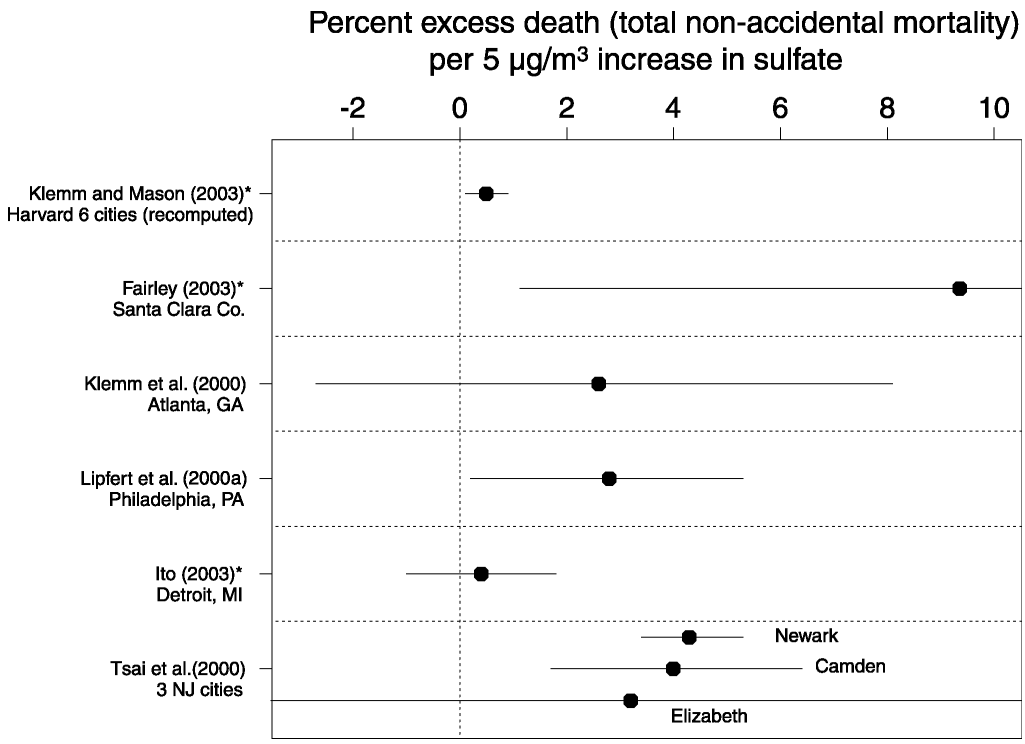

Figure 9-17. Relative risks estimated per 5-µg/m^3 increase in sulfate from U.S. and Canadian studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

source profiles for $PM_{2.5}$ in western cities is that it allows separation of crustal PM from accumulation-mode PM derived from anthropogenic origins.

Several new studies highlighted in Chapter 8 conducted source-category-oriented evaluations of PM components using factor analysis (see Table 9-9). The results of these studies (Laden et al., 2000; Mar et al., 2000; Tsai et al., 2000; Özkaynak et al., 1996) generally suggest that a number of combustion-related source-categories are associated with excess mortality risk, including: regional sulfate; automobile emissions; coal combustion; oil burning; and vegetative (biomass) burning. In contrast, the crustal factor from fine particles was generally not positively associated with total mortality, with Mar et al. (2000) reporting a negative association between the crustal component of $PM_{2.5}$ and cardiovascular mortality.

However, these source-category-oriented evaluation results are derived from relatively limited underlying analytic bases for resolving source categories and the identification of source

TABLE 9-9. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PM COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality (Comments)
Laden et al., (2000); Schwartz (2003)* Harvard Six Cities. 1979-1988.	*Soil and crustal material*: Si *Motor vehicle emissions:* Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality was associated with the mobile source factor. Coal combustion factor was also positively associated with mortality. Crustal factor from fine particles not associated (negative but not significant) with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000, 2003)* Phoenix, AZ. 1995-1997.	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust:* Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and K_S (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S	*$PM_{2.5}$ factors results:* Motor vehicle factor (1 day lag), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were significantly positively associated with cardiovascular mortality.
	$PM_{10-2.5}$ (from dichot) trace elements: *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	Factors from dichot $PM_{10-2.5}$ trace elements not analyzed for their associations with mortality because of the small sample size (every 3rd-day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions:* Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.
Ozkaynak 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.

*Note: The study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms, but was later reanalyzed using more stringent convergence criteria and/or other approaches.

categories must be viewed with caution at this time. Nevertheless, although somewhat limited at this time, the new factor analysis results appear to implicate ambient PM derived from fossil fuel (oil, coal) combustion and vegetative burning, as well as secondarily formed sulfates, as important contributors to observed mortality effects, but not crustal particles.

In summary, the new evidence suggests that exposure to particles from several different source categories, and of different composition and size, may have independent associations with health outcomes. The excess risks from different types of combustion sources (coal, oil, gasoline, wood, and vegetation) may vary from place to place and from time to time, so that some intra-regional and inter-regional heterogeneity would be expected. Likewise, although earlier evaluations in the 1996 PM AQCD seemed to indicate coarse particles and intermodal particles of crustal composition as not likely being associated with adverse health effects, there are now some reasonably credible studies suggesting that coarse particles (although not necessarily those of crustal composition) may be associated with excess mortality in at least some locations. These notably include areas where past deposition of fine PM metals from smelter (Phoenix) or steel mills (Steubenville) onto surrounding soils may result in enhanced toxicity of later resuspended coarse ($PM_{10-2.5}$) particles.

Relationships of Ambient Particulate Matter Concentrations to Morbidity Outcomes

New epidemiology studies add greatly to the overall database relating morbidity outcomes to ambient PM levels. These include much additional evidence for cardiovascular and respiratory diseases being related to ambient PM. The newer epidemiology studies expand the evidence on cardiovascular (CVD) disease and are discussed first below, followed by discussion of respiratory disease effects with particular emphasis on newly enhanced evidence for PM-asthma relationships. Table 9-10 summarizes cardiovascular and respiratory-related morbidity effect size estimates for variable increments in PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ concentrations for studies of U.S. and Canadian cities.

Cardiovascular Effects of Ambient Particulate Matter Exposures

Cardiovascular Hospital Admissions. Just two studies were available for review in the 1996 PM AQCD that provided data on acute cardiovascular morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time series design using standard statistical methods. Analyzing 4 years of data on the ≥ 65-year-old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett and

TABLE 9-10. CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m³ PM_{10} Increase	% increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
CARDIOVASCULAR MORBIDITY					
Total Cardiovascular Hospital Admissions:					
Samet et al. (2000a,b) 14 U.S. Cities (> 65 years) Zanobetti and Schwartz (2003)	strict GAM GLM NS GLM PS	4.95% (3.95-5.95) 4.8% (3.55-6.0) 5.0% (4.0-5.95)	—	—	PM_{10} means 24.4-45.3
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	3.25% (2.04, 4.47)	—	—	PM_{10} 45.5 (5, 132)
Moolgavkar (2000b) Moolgavkar (2003) Cook Co., IL (> 65 years)	strict GAM_{100df} GLM NS_{100df}	4.05% (2.9-5.2) 4.25% (3.0-5.5)	—	—	PM_{10} median 35 (3, 365)
Moolgavkar (2000b) Moolgavkar (2003) Los Angeles, CA (> 65 years)	GAM_{30df} GAM_{100df} GLM NS_{100df}	3.35% (1.2-5.5) 2.7% (0.6-4.8) 2.75% (0.1-5.4)	3.95% (2.2-5.7) 2.9% (1.2-4.6) 3.15% (1.1-5.2)	—	PM_{10} median 44 (7, 166) $PM_{2.5}$ median 22 (4, 86)
Morris and Naumova (1998) Chicago, IL (> 65 years)	GAM not used	3.92 (1.02, 6.90)	—	—	PM_{10} 41 (6, 117)
Tolbert et al., (2000a) Atlanta, GA 1993-1998	GAM not used	−8.2% (p = 0.002)	—	—	Period 1 PM_{10} 30.1 (SD 12.4)
Tolbert et al. (2000a) Atlanta, GA (all ages)	GAM not used	5.1 (−7.9, 19.9)	6.1 (−3.1, 16.2)	17.6 (−4.6, 45.0)	PM_{10} 29.1 (SD 12.0) $PM_{2.5}$ 19.4 (SD 9.35) $PM_{10-2.5}$ 9.39 (SD 4.52)
Stieb et al. (2000) St. John, CAN (all ages)	GAM not used	39.2 (5.0, 84.4)	15.11 (0.61, 11.03)#	—	summer 93 PM_{10} 14.0 (max 70.3) $PM_{2.5}$ 8.5 (max 53.2)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Total Cardiovascular Hospital Admissions: (cont'd)					
Burnett et al. (1997) Toronto, CAN (all ages)	GAM not used	12.07 (1.43, 23.81)#	7.18 (−0.61, 15.60)#	20.46 (8.24, 34.06)#	PM_{10} 28.4 (4, 102) $PM_{2.5}$ 16.8 (1, 66) $PM_{10-2.5}$ 11.6 (1, 56)
Ischemic Heart Disease Hospital Admissions:					
Lippmann et al. (2000) Detroit, MI (> 65 years) Ito 2003	Strict GAM GLM NS	8.0% (−0.3-17.1) 6.2% (−2.0-15.0)	3.65% (−2.05-9.7) 3.0% (−2.7-9.0)	10.2% (2.4-18.6) 8.1% (0.4-16.4)	PM_{10} 31 (max 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50)
Dysrhythmias Hospital Admissions:					
Tolbert et al. (2000a) Atlanta, GA (all ages)	GAM not used	13.41 (−14.08, 48.99)	6.11 (−12.63, 28.86)	53.16 (2.07, 129.81)	$PM_{2.5}$ 19.4 (SD 9.35) $PM_{10-2.5}$ 9.39 (SD 4.52)
Lippmann et al. (2000) Detroit, MI (> 65 years) Ito (2003)	Strict GAM GLM NS	2.8% (−10.9-18.7) 2.0% (−11.7-17.7)	3.2% (−6.6-14.0) 2.6% (−7.1-13.3)	0.1% (−12.4-14.4) 0.0% (−12.5-14.3)	PM_{10} 31 (max 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50)
Heart Failure Hospital Admissions:					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	2.02 (−0.94, 5.06)	—	—	PM_{10} 45.5 (5, 132)
Lippmann et al. (2000) Ito (2003) Detroit, MI (> 65 years)	Strict GAM GLM NS	9.2% (−0.3-19.6) 8.4% (−1.0-18.7)	8.0% (1.4-15.0) 6.8% (0.3-13.8)	4.4% (−4.0-13.5) 4.9% (−3.55-14.1)	PM_{10} 31 (max 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50)
Myocardial Infarction Hospital Admissions:					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	3.04 (0.06, 6.12)	—	—	PM_{10} 45.5 (5, 132)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Cardiac arrhythmia Hospital Admissions:					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	1.01 (−1.93, 4.02)	—	—	PM_{10} 45.5 (5, 132)
Cerebrovascular Hospital Admissions:					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	0.30 (−2.13, 2.79)	—	—	PM_{10} 45.5 (5, 132)
Stroke Hospital Admissions:					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	6.72 (3.64, 9.90)	—	—	PM_{10} 45.5 (5, 132)
RESPIRATORY MORBIDITY					
Total Respiratory Hospital Admissions:					
Thurston et al. (1994) Toronto, Canada	GAM not used	23.26 (2.03, 44.49)	15.00 (1.97, 28.03)	22.25 (−9.53, 54.03)	PM_{10} 29.5-38.8 (max 96.0) $PM_{2.5}$ 15.8-22.3 (max 66.0) $PM_{10-2.5}$ 12.7-16.5 (max 33.0)
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	2.89 (1.09, 4.72)	—	—	PM_{10} 45.5 (5, 132)
Schwartz et al. (1996) Cleveland, OH (> 65 years)	GAM not used	5.8 (0.5, 11.4)	—	—	PM_{10} 43
Lumley and Heagerty (1999) King County, WA (all ages)	GAM not used	—	5.91 (1.10, 10.97)	—	PM_1 NR

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Total Respiratory Hospital Admissions: (cont'd)					
Burnett et al. (1997) Toronto, CAN (all ages)	GAM not used	10.93 (4.53, 17.72)	8.61 (3.39, 14.08)	12.71 (5.33, 20.74)	PM_{10} 28.1 (4, 102) $PM_{2.5}$ 16.8 (1, 66) $PM_{10-2.5}$ 11.6 (1, 56)
Delfino et al. (1997) Montreal, CAN (> 64 years)	GAM not used	36.62 (10.02, 63.21)	23.88 (4.94, 42.83)	—	summer 93 PM_{10} 21.7 (max 51) $PM_{2.5}$ 12.2 (max 31)
Delfino et al. (1998) Montreal, CAN (> 64 years)	GAM not used	—	13.17 (−0.22, 26.57)	—	$PM_{2.5}$ 18.6 (SD 9.3)
Stieb et al. (2000) St. John, CAN (all ages)	GAM not used	8.8 (1.8, 16.4)	5.69 (0.61, 11.03)	—	summer 93 PM_{10}14.0 (max 70.3) $PM_{2.5}$ 8.5 (max 53.2)
Pneumonia Hospital Admissions:					
Samet et al. (2000a,b) 14 U.S. Cities (> 65 years) Zanobetti and Schwartz (2003)	Strict GAM GLM NS GLM PS	8.8 (5.9, 11.8) 2.9 (0.2, 5.6) 6.3 (2.5, 10.3)	—	—	PM_{10} means 24.4-45.3
Lippmann et al. (2000) Detroit, MI (> 65 years) Ito (2003)	Strict GAM GLM NS	18.1 (5.3, 32.5) 18.6 (5.6, 33.1)	10.5 (1.8, 19.8) 10.1 (1.5, 19.5)	9.9 (−0.1, 22.0) 11.2 (−0.02, 23.6)	PM_{10} 31 (max 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50)
COPD Hospital Admissions:					
Samet et al. (2000a,b) 14 U.S. Cities (> 65 years) Zanobetti and Schwartz (2003)	Strict GAM GLM NS GLM PS	8.8 (4.8, 13.0) 6.8 (2.8, 10.8) 8.0 (4.3, 11.9)	—	—	PM_{10} means 24.4-45.3

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
COPD Hospital Admissions (cont'd)					
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	1.5 (−0.5, 3.5)	—	—	PM_{10} 45.5 (5, 132)
Tolbert et al. (2000a) Atlanta, GA (all ages)	GAM not used	−3.5 (33.0, −29.9)	12.44 (−7.89, 37.24)	−23.03 (−50.69, 20.15)	PM_{10} 29.1 (SD 12.0) $PM_{2.5}$ 19.4 (SD 9.35) $PM_{10-2.5}$ 9.39 (SD 4.52)
Lippmann et al. (2000) Detroit, MI (> 65 years) Ito (2003)	Strict GAM GLM NS	6.5 (−7.8, 23.0) 4.6 (−9.4, 20.8)	3.0(−6.9, 13.9) 0.3(−9.3, 10.9)	8.7 (−4.8, 24.0) 10.8 (−3.1, 26.5)	PM_{10} 31 (max 105) $PM_{2.5}$ 18 (6, 86) $PM_{10-2.5}$ 13 (4, 50)
Moolgavkar (2000c) Cook Co., IL (> 65 years) Moolgavkar 2003	Strict GAM: 100df	3.24 (.031, 6.24)	—	—	PM_{10} median 35 (3, 365)
Moolgavkar (2000c) Los Angeles, CA (> 65 years) Moolgavkar 2003	Strict GAM: 100df GLM NS: 100df	5.52 (2.53-8.59) 5.00 (1.22, 8.91)	2.87 (0.53, 5.27) 2.59 (−0.29, 5.56)		PM_{10} median 44 (7, 166) $PM_{2.5}$ median 224, 86) $PM_{10-2.5}$ NR
Asthma Hospital Admissions:					
Choudbury et al. (1997) Anchorage, AK Medical Visits (all ages)	GAM not used	20.9 (11.8, 30.8)	—	—	PM_{10} 42.5 (1, 565)
Jacobs et al. (1997) Butte County, CA (all ages)	GAM not used	6.11 (p > 0.05)	—	—	PM_{10} 34.3 (6.6, 636)
Linn et al. (2000) Los Angeles, CA (> 29 years)	GAM not used	1.5 (-2.4, 5.6)	—	—	PM_{10} 45.5 (5, 132)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Asthma Hospital Admissions: (cont'd)					
Lipsett et al. (1997) Santa Clara Co., CA (all ages)	GAM not used	34.7 (16, 56.5) (at 20° F)	—	—	PM_{10} 61.2 (9, 165)
Nauenberg and Basu (1999) Los Angeles, CA (all ages)	GAM not used	20.0 (5.3, 35)	—	—	44.8 (SE 17.23)
Tolbert et al. (2000b) Atlanta, GA (< 17 years)	GAM not used	13.2 (1.2, 26.7)	—	—	PM_{10} 38.9 (9, 105)
Tolbert et al. (2000a) Atlanta, GA (all ages)	GAM not used	18.8 (−8.7, 54.4)	2.3 (−14.8, 22.7)	21.1 (−18.2, 79.3)	PM_{10} 29.1 (SD 12.0) $PM_{2.5}$ 19.4 (SD 9.35) $PM_{10-2.5}$ 9.39 (SD 4.52)
Sheppard et al. (1999) Seattle, WA (< 65 years)	Strict GAM GLM NS	10.9 (2.8, 19.6) 8.1 (0.1, 16.7)	8.7 (3.2, 14.4) 6.5 (1.1,12.0)	5.5 (0, 14.0) 5.5 (−2.7, 11.1)	PM_{10} 31.5 (90% 55) $PM_{2.5}$ 16.7 (90% 32) $PM_{10-2.5}$ 16.2 (90% 29)
Respiratory Symptoms		Odds Ratio (95% CI) for 50 ug/m^3 increase in PM_{10}	Odds Ratio (95% CI) for 25 ug/m^3 increase in $PM_{2.5}$	Odds Ratio (95% CI) for 25 ug/m^3 increase in $PM_{10-2.5}$	$PM_{10-2.5}$ Mean (Range) Levels Reported**
Schwartz et al. (1994) 6 U.S. cities (children, cough)	GAM not used	1.39 (1.05, 1.85)	1.24 (1.00, 1.54)	—	PM_{10} median 30.0 (max 117) $PM_{2.5}$ median 18.0 (max 86)
Schwartz et al. (1994) 6 U.S. cities (children, lower respiratory symptoms)	GAM not used	2.03 (1.36, 3.04)	1.58 (1.18, 2.10)	—	PM_{10} median 30.0 (max 117) $PM_{2.5}$ median 18.0 (max 86)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Respiratory Symptoms (cont'd)					
Neas et al. (1995) Uniontown, PA (children, cough)	GAM not used	—	2.45 (1.29, 4.64)	—	$PM_{2.5}$ 24.5 (max 88.1)
Ostro et al. (1991) Denver, CO (adults, cough)	GAM not used	1.09 (0.57, 2.10)	—	—	PM_{10} 22 (0.5, 73)
Pope et al. (1991) Utah Valley, UT (lower respiratory symptoms, schoolchildren)	GAM not used	1.28 (1.06, 1.56)	—	—	PM_{10} 44 (11, 195)
Pope et al. (1991) Utah Valley, UT (lower respiratory symptoms, asthmatic patients)	GAM not used	1.01 (0.81, 1.27)	—	—	PM_{10} 44 (11, 195)
Neas et al. (1996) State College, PA (children, cough)	GAM not used	NR	1.48 (1.17, 1.88) (1-d)	—	PM_{10} 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8)
Neas et al. (1996) State College, PA (children, wheeze)	GAM not used	NR	1.59 (0.93, 2.70) (1-d)	—	PM_{10} 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8)
Neas et al. (1996) State College, PA (children, cold)	GAM not used	NR	1.61 (1.21, 2.17) (0-d)	—	PM_{10} 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8)
Ostro et al. (1995) Los Angeles, CA (children, asthma episode)	GAM not used	1.05 (0.64, 1.73)	—	—	PM_{10} 55.87 (19.63, 101.42)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Respiratory Symptoms (cont'd)					
Ostro et al. (1995) Los Angeles, CA (children, shortness of breath)	GAM not used	1.51 (1.04, 2.17)	—	—	PM_{10} 55.87 (19.63, 101.42)
Schwartz and Neas (2000) Six Cities reanalysis (children, cough)	GAM not used		1.28 (0.98, 1.67)	1.77 (1.23, 2.54)	$PM_{2.5}$ (same as Six Cities) $PM_{10-2.5}$ NR
Schwartz and Neas (2000) Six Cities reanalysis (children, lower respiratory symptoms)	GAM not used	—	1.61 (1.20, 2.16)	1.51 (0.66, 3.43)	$PM_{2.5}$ (same as Six Cities) $PM_{10-2.5}$ NR
Vedal et al. (1998) Port Alberni, CAN (children, cough)	GAM not used	1.40 (1.14, 1.73)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, phlegm)	GAM not used	1.40 (1.03, 1.90)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, nose symptoms)	GAM not used	1.22 (1.00, 1.47)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, sore throat)	GAM not used	1.34 (1.06, 1.69)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, wheeze)	GAM not used	1.16 (0.82, 1.63)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Respiratory Symptoms (cont'd)					
Vedal et al. (1998) Port Alberni, CAN (children, chest tightness)	GAM not used	1.34 (0.86, 2.09)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, dyspnea)	GAM not used	1.05 (0.74, 1.49)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Vedal et al. (1998) Port Alberni, CAN (children, any symptom)	GAM not used	1.16 (1.00, 1.34)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)
Lung Function Changes		Lung Function change (L/min) (95% CI) for 50 ug/m^3 increase in PM_{10}	Lung Function change (L/min) (95% CI) for 25 ug/m^3 increase in $PM_{2.5}$	Lung Function change (L/min) (95% CI) for 25 ug/m^3 increase in $PM_{10-2.5}$	$PM_{10-2.5}$ Mean (Range) Levels Reported**
Neas et al. (1995) Uniontown, PA (children)	GAM not used	—	−2.58 (−5.33, +0.35)	—	$PM_{2.5}$ 24.5 (max 88.1)
Thurston et al. (1997) Connecticut summer camp (children)	GAM not used	—	PEFR −5.4 (−12.3, 1.5) (15 μg/m^3 $SO_4^=$)	—	$SO_4^=$ 7.0 (1.1, 26.7)
Naeher et al. (1999) Southwest VA (adult women)	GAM not used	am PEFR −3.65 (−6.79, −0.51) pm PEFR −1.8 (−5.03, 1.43)	am PEFR −1.83 (−3.44, −0.21) pm PEFR −1.05 (−2.77, 0.67)	am PEFR −6.33 (−12.50, −0.15) pm PEFR −2.4 (−8.48, 3.68)	PM_{10} 27.07 (4.89, 69.07) $PM_{2.5}$ 21.62 (3.48, 59.65) $PM_{10-2.5}$ 5.72 (0.00, 19.78)
Neas et al. (1996) State College, PA (children)	GAM not used	—	pm PEFR −0.64 (−1.73, 0.44)	—	$PM_{2.5}$ 23.5 (max 85.8)

DRAFT-DO NOT QUOTE OR CITE

TABLE 9-10 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

Original study* Reanalysis study Study location	Analysis Comments**	% increase (95% CI) per 50 μg/m^3 PM_{10} Increase	% increase (95% CI) per 25 μg/m^3 $PM_{2.5}$ Increase	% increase (95% CI) per 25 μg/m^3 $PM_{10-2.5}$ Increase	PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported***
Lung Function Changes (cont'd)					
Neas et al. (1999) Philadelphia, PA (children)	GAM not used	am PEFR −8.17 (−14.81, −1.56) pm PEFR −1.44 (−7.33, 4.44)	am PEFR −3.29 (−6.64, 0.07) pm PEFR −0.91 (−4.04, 2.21)	am PEFR −4.31 (−11.44, 2.75) pm PEFR 1.88 (−4.75, 8.44)	$PM_{2.5}$ 22.2 (IQR 16.2) $PM_{10-2.5}$ 9.5 (IQR 5.1)
Schwartz and Neas (2000) Uniontown, PA (reanalysis) (children)	GAM not used	—	pm PEFR −1.52, (−2.80, −0.24)	pm PEFR +1.73 (−2.2, 5.67)	$PM_{2.5}$ 24.5 (max 88.1) $PM_{10-2.5}$ NR
Schwartz and Neas (2000) State College PA (reanalysis) (children)	GAM not used	—	pm PEFR −0.93 (−1.88, 0.01)	pm PEFR −0.28 (−3.45, 2.87)	$PM_{2.5}$ 23.5 (max 85.8) $PM_{10-2.5}$ NR
Vedal et al. (1998) Port Alberni, CAN (children)	GAM not used	PEF −1.35 (−2.7, −0.05)	—	—	PM_{10} median 22.1 (0.2, 159.0) (north site)

* Both original published studies and recent reanalyses reported in HEI (2003) Special Report for many cited here. Original studies published before 1996 and Schwartz et al. (1996) were assessed in 1996 PM AQCD.

** Where GAM not used in original analysis cited, original results reported here. Otherwise reanalyses results reported here if GAM (default) used in original analysis. GAM strict = GAM with stringent criteria. GLM = general linear model; NS = natural splines; BS = B splines; PS = penalized splines.

*** Mean (minimum, maximum) 24-h PM level in parentheses unless otherwise noted.

DRAFT-DO NOT QUOTE OR CITE

colleagues (1995) reported significant associations between particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk because of sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that, "There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints." The PM AQCD went on to state that acute impacts on CVD admissions had been demonstrated for elderly populations (i.e., $\geq$ 65), but that insufficient data existed to assess relative impacts on younger populations.

Although the literature still remains relatively sparse, an important new body of data now exists that both extends the available quantitative information on relationships between ambient PM pollution and hospital CVD admissions, and that, more intriguingly, illuminates some of the physiological changes that may occur on the mechanistic pathway leading from PM exposure to adverse cardiac outcomes. Results of these new findings (including from GAM reanalyses) are summarized in Table 9-10; and Figure 9-18 depicts excess risk estimates derived from several studies of acute PM_{10} exposure effects on CVD admissions in U.S. cities. Although new studies depicted in Figure 9-17 have reported generally consistent associations between daily hospitalizations for cardiovascular disease and measures of PM, the data not only implicate PM, but also CO and NO_2 as well, possibly because of covarying of PM and these other gaseous pollutants derived from common emission sources (e.g., motor vehicles). Taken as a whole, this body of evidence suggests that PM is likely an important risk factor for cardiovascular hospitalizations in the United States.

The NMMAPS study of PM_{10} concentrations and hospital admissions by persons 65 and older in 14 U.S. cities provides particularly important findings of positive and significant associations, even when concentrations are below 50 $\mu g/m^3$ (Samet et al., 2000a,b; and reanalyses by Zanobetti and Schwartz, 2003b). As noted in Table 9-10 and Figure 9-18, this study indicates PM_{10} CVD hospitalization effects similar to other cities, but with narrower confidence bands, because of its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each of the 14 cities had mean PM_{10} below 50 $\mu g/m^3$.

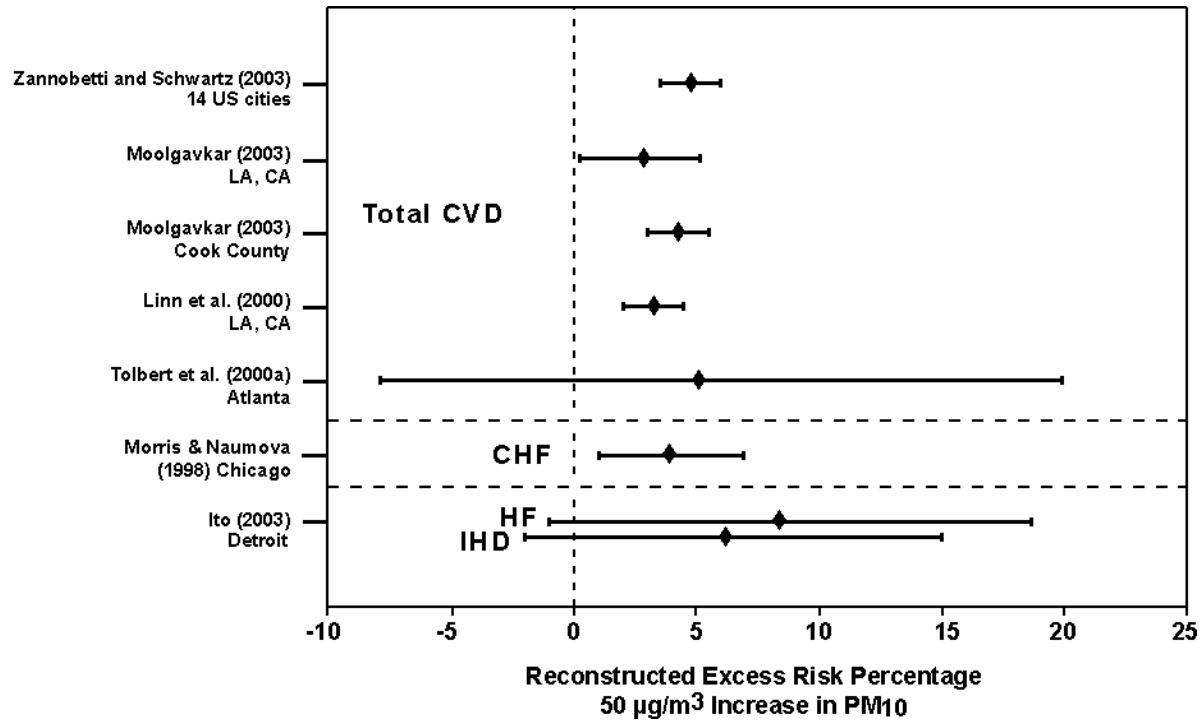

Figure 9-18. Acute cardiovascular hospitalizations and PM exposure excess risk estimates derived from selected U.S. PM_{10} studies. CVD = cardiovascular disease and CHF = congestive heart failure.

Several new studies have evaluated fine and coarse fraction particle effects on CVD hospital admissions, with mixed overall results. That is, most all of the studies found positive associations between $PM_{2.5}$ or $PM_{10\text{-}2.5}$ and increased CVD hospitalizations (Moolgavkar, 2000b; reanalysis Moolgavkar, 2003; Tolbert et al., 2000a; Lippmann et al., 2000; reanalysis Ito, 2003; Burnett et al., 1997; Stieb et al., 2000). Excess risks generally fell in the range of ~3.0 to 8.0% per 25 µg $PM_{2.5}$ (24-h) increment; however, only a few were statistically significant at $p < 0.05$. The $PM_{10\text{-}2.5}$ CVD admissions results all showed positive associations as well, but the RR values spanned a much wider range, from ~ 0.0% on up to ~20% per 25 $\mu g/m^3$; and several were statistically significant at $p < 0.05$. Thus, no clear evidence emerged for stronger associations with fine versus coarse fraction short-term PM exposures.

Physiologic Measures of Cardiac Function. Several studies by independent groups of investigators have also reported longitudinal associations between ambient PM concentrations and physiologic measures of cardiovascular function. These studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions about individual risks, as well as to explore mechanistic hypotheses. Such studies, for example, have reported temporal associations between PM exposures and various electrocardiogram (ECG) measures of heart beat or rhythm in panels of elderly subjects. Reduced HR variability is a predictor of increased cardiovascular morbidity and mortality risks. Three independent studies reported decreases in HR variability associated with PM in elderly cohorts, although r-MSSD (one measure of high-frequency HR variability) only showed elevations with PM in one study. Differences in methods used and results across the studies argue for caution in drawing any strong conclusions regarding PM effects from them, especially in light of the complex intercorrelations that exist among measures of cardiac physiology, meteorology, and air pollution (Dockery et al., 1999). Still, the new heart rhythm results, in general, comport well with other findings of cardiovascular mortality and morbidity endpoints being associated with ambient PM. Chapter 5 discusses available exposure studies of elderly subjects with CVD, such as the Sarnat et al. (2000) Baltimore study. Less active groups tend to have lower exposure to nonambient PM because of reduced personal activity. However, Williams et al. (2000a,b,c) report a very high pooled correlation coefficient between $PM_{2.5}$ personal exposure and outdoor concentrations. These exposure studies tend to enhance the plausibility of panel study findings of impacts on HR variability being caused by exposure to ambient-generated PM.

Changes in Blood Characteristics. Additional epidemiologic findings (Peters et al., 1997a) also provide new evidence for ambient PM exposure effects on blood characteristics (e.g., increased c-reactive protein in blood) thought to be associated with increased risk of serious cardiac outcomes (e.g., heart attacks).

Key Conclusions Regarding PM-CVD Morbidity

Overall, the newly available studies of PM-CVD relationships appear to support the following conclusions regarding several key issues:

(1) Temporal Patterns of Response. The evidence from recent time series studies of CVD admissions suggests rather strongly that PM effects are likely maximal at lag 0, with some carryover to lag 1.

(2) Physical and Chemical Attributes Related to Particulate Matter Health Effects. The characterization of ambient PM attributes associated with acute CVD is incomplete. Insufficient data exist from the time series CVD hospital admissions literature or from the emerging individual-level studies to provide clear guidance as to which PM attributes, defined either on the basis of size or composition, determine potency. The epidemiologic studies published to date have been constrained by the limited availability of multiple PM metrics. Where multiple PM metrics exist, they often are of differential quality because of differences in numbers of monitoring sites and in monitoring frequency. Until more extensive and consistent data become available for epidemiologic research, the question of PM size and composition, as they relate to acute CVD impacts, will remain open.

(3) Susceptible Subpopulations. Because they lack data on individual subject characteristics, ecologic time series studies provide only limited information on susceptibility factors based on stratified analyses. The relative impact of PM on cardiovascular (and respiratory) admissions reported in ecologic time series studies is generally somewhat higher than those reported for total admissions. This provides some support for the hypothesis that acute effects of PM operate via cardiopulmonary pathways or that persons with preexisting cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from the ecologic time series studies showing larger relative impacts of PM on cardiovascular admissions in adults 65 and over as compared with younger populations, the differences are neither striking nor consistent. Some individual-level studies of cardiophysiologic function suggest that elderly persons with preexisting cardiopulmonary disease are susceptible to subtle changes in heart rate variability (HRV) in association with PM exposures. However, because younger and healthier populations have not yet been assessed, it is not possible to say at present whether the elderly have clearly increased susceptibility compared to other groups, as indexed by cardiac pathophysiological indices such as HRV.

(4) Role of Other Environmental Factors. The ecologic time series morbidity studies published since 1996 generally have controlled adequately for weather influences. Thus, it is unlikely that residual confounding by weather accounts for the PM associations observed. With one possible exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac physiologic function. Thus, the possibility of confounding in such studies as yet cannot be discounted totally or readily. Co-pollutants have been analyzed rather extensively in many of the recent time series studies of hospital admissions and PM. In some studies, PM clearly carries an independent association after controlling for gaseous co-pollutants. In others, the "PM effects" are reduced markedly once co-pollutants are added to the model. Among the gaseous criteria pollutants, CO has emerged as the most consistently associated with cardiovascular (CVD) hospitalizations. The CO effects are generally robust in the multi-pollutant model, sometimes as much so as PM effects. However, the typically low levels of ambient CO concentrations in most such studies and minimal expected consequent impacts on carboxyhemoglobin levels and associated hypoxic effects thought to underlie CO CVD effects argue for the likelihood that CO may be serving as a general surrogate for combustion products (e.g., PM) in the ambient pollution mix. See the most recent EPA CO Criteria Document (U.S. Environmental Protection Agency, 2000a).

Respiratory Effects of Ambient Particulate Matter Exposures

The number of studies examining hospitalization and emergency department visits for respiratory-related causes and other respiratory morbidity endpoints has increased markedly since the 1996 PM AQCD. In addition to evaluating statistical relationships for PM_{10}, quite a few new studies also evaluated other PM metrics. Those providing estimates of increased risk in U.S. and Canadian cities for respiratory-related morbidity measures (hospitalizations, respiratory symptoms, etc.) in relation to 24-h increments in ambient fine particles ($PM_{2.5}$) or coarse fraction ($PM_{10-2.5}$) of inhalable thoracic particles are included in Table 9-10.

Respiratory-Related Hospital Admission/Visits. Hospital admissions/ visit studies that evaluated excess risks in relation to PM_{10} measures are still quite informative. Maximum excess

risk estimates for PM_{10} associations with respiratory-related hospital admissions and visits in U.S. cities are shown in Figure 9-19. Nearly all the studies showed positive, statistically significant relationships between ambient PM_{10} and increased risk for respiratory-related doctors' visits and hospital admissions. Overall, the results substantiate well ambient PM_{10} impacts on respiratory-related hospital admissions/visits. The excess risk estimates fall most consistently in the range of 5 to 25.0% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma hospital admissions and doctor's visits being higher than for COPD and pneumonia hospitalization. Other, more limited, new evidence (not depicted in Figure 9-19) shows excess risk estimates for overall respiratory-related or COPD hospital admissions falling mainly in the range of ~3.0 to 24% per 24-h 25 $\mu g/m^3$ increment in $PM_{2.5}$ or $PM_{10-2.5}$. Analogous estimates were found for asthma admissions or physician visits, ranging up to ca. From ~2.0 to 22.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ or $PM_{10-2.5}$ increment.

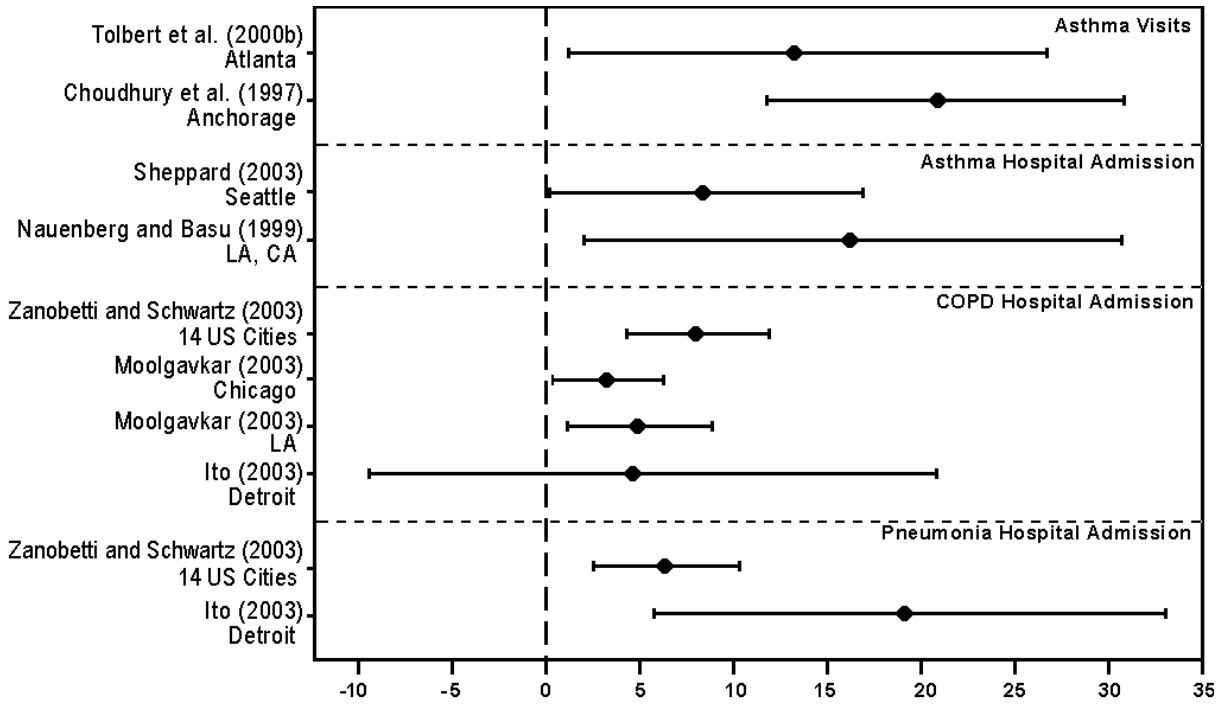

Figure 9-19. Maximum excess risk in selected studies of U.S. cities relating PM_{10} estimate of exposure (50 $\mu g/m^3$) to respiratory-related hospital admissions and visits.

Of particular note in Figure 9-19 are the large effect size estimates now being reported for asthma hospitalizations and visits. Very importantly, these hospital admission/visit studies and other new studies on respiratory symptoms and lung function decrements in asthmatics are emerging as possibly indicative of ambient PM likely being a notable contributor to exacerbation of asthma.

Pulmonary Function Changes and Respiratory Symptoms. Additional evidence for PM-asthma effects is also emerging from panel studies of lung function and respiratory symptoms. New panel studies of lung function and respiratory symptoms in asthmatic subjects have been conducted by more than 10 research teams in various locations world-wide. As a group, the studies examine health outcome effects that are similar, such as pulmonary peak flow rate (PEFR); and the studies typically characterize the clinical-symptomatic aspects in a sample of mild to moderate asthmatics (mainly children aged 5 to 16 yrs) observed in their natural setting. Their asthma typically is being treated to keep them symptom free (with "normal" pulmonary function rates, and activity levels) and to prevent recurrent exacerbations of asthma. Severity of their asthma is characterized by symptom, pulmonary function, and medication use and would be classified to include mild intermittent to mild persistent asthma suffers (National Institutes of Health, 1997). As a group, they may thusly differ from asthmatics examined in studies of hospitalization or doctor visits for acute asthmatic episodes, who may have more severe asthma.

Most studies reported ambient PM_{10} results, but $PM_{2.5}$ was examined in two studies. Other ambient PM measures (BS and SO_4) also were used. For these studies, mean PM_{10} levels range from a low of 13 $\mu g/m^3$ in Finland to a high of 167 $\mu g/m^3$ in Mexico City. The Mexico City level is over three times more than each of the other levels and is unique compared to the others. Related 95% CI for these means or ranges show 1-day maximums above 100 $\mu g/m^3$ in four studies, with two of these above 150 $\mu g/m^3$. Hence, these studies mainly evaluated different PM metrics indexing PM concentrations in the range found in U.S. cities (see Chapter 3). All the studies controlled for temperature, and several controlled for relative humidity.

Many panel studies are analyzed using a design that takes advantage of the repeated measures on the same subject. Study subject number (N) varied from 12 to 164, with most having $N > 50$; and all gathered adequate subject-day data to provide sufficient power for their

analyses. Linear models often are used for lung function and logistic models for dichotomous outcomes. Meteorological variables are used as covariates; and medication use is also sometimes evaluated as a dependent variable or treated as an important potential confounder. However, perhaps the most critical choice in the model is selection of the lag for the pollution variable. Presenting lag periods with only the strongest associations introduces potential bias, because the biological basis for lag structure may be related to effect. No biological bases for pertinent lag periods are known, but some hypotheses can be proposed. Acute asthmatic reactions can occur 4 to 6 h after exposure and, thus, 0-day lag may be more appropriate than 1-day lags for that acute reaction. Lag 1 may be more relevant for morning measurement of asthma outcome from PM exposure the day before, and longer term lags (i.e., 2 to 5 days) may represent the outcome of a more prolonged inflammatory mechanism; but too little information is now available to predetermine appropriate lag(s).

Chapter 8 noted that people with asthma tend to have greater TB deposition than do healthy people, but this data was not derived from the younger age group studied in most asthma panel studies. The Peters et al. (1997b) study is unique for two reasons: (1) they studied the size distribution of the particles in the range 0.01 to 2.5 μm and (2) examined the number of particles. They reported that asthma-related health effects of 5-day means of the number of ultrafine particles were larger than those of the mass of the fine particles. In contrast, Pekkanen et al. (1997) also examined a range of PM sizes, but PM_{10} was more consistently associated with PEF. Delfino et al. (1998) is unique in that they report larger effects for 1- and 8-h maximum PM_{10} than for the 24-h mean.

The results for the asthma panels of the peak flow analysis consistently show small decrements for both PM_{10} and $PM_{2.5}$. The effects using 2- to 5-day lags averaged about the same as did the 0 to 1 day lags. Stronger relationships often were found with ozone. The analyses were not able to clearly separate co-pollutant effects. The effects on respiratory symptoms in asthmatics also tended to be positive. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use. The only endpoint more strongly related to longer lag times was bronchodilator use, which was observed in three studies. The peak flow decrements and respiratory symptoms are indicators for asthma episodes.

For PM_{10}, nearly all of the point estimates for PEF showed decreases, but most were not statistically significant, as shown in Figure 9-20 as an example of PEF outcomes. Lag 1 may be

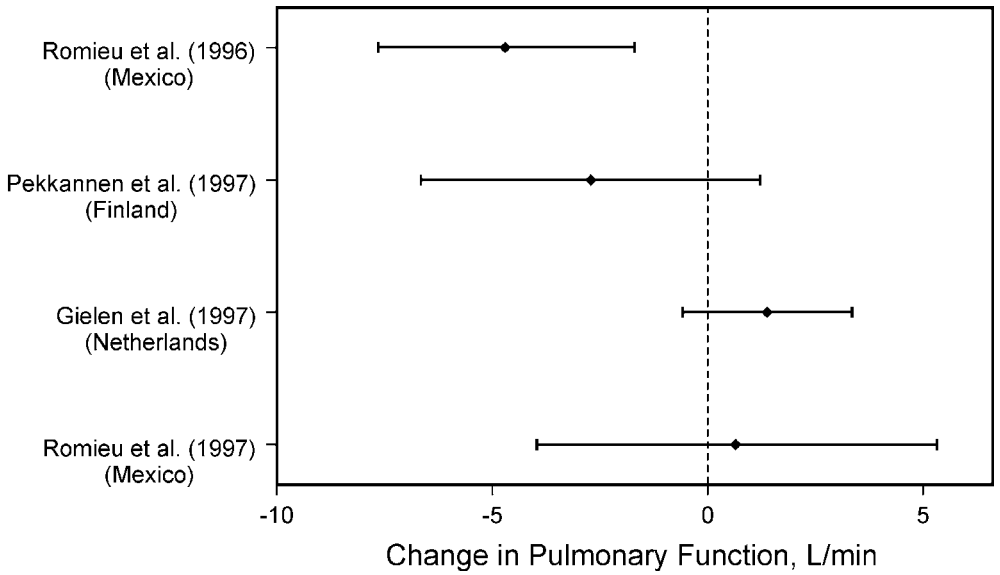

Figure 9-20. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 µg/m^3 PM_{10} on morning peak flow lagged 1 day.

more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies that provided this data. The results were consistent for both AM and PM peak flow analyses. Similar results were found for the $PM_{2.5}$ studies, although there were fewer studies. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Gold et al. (1999), Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al. (1997), and Romieu et al. (1996) all found similar results for $PM_{2.5}$ and PM_{10}. The study of Peters et al. (1997b) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas (2000) found larger effects for $PM_{2.5}$ than for $PM_{10-2.5}$. Naeher et al. (1999) found that H^+ was related significantly to a decrease in morning PEF. Thus, there is no evidence here for a stronger effect of $PM_{2.5}$ when compared to PM_{10}. Also, of studies that provided analyses that attempted to separate out effects of PM_{10} and $PM_{2.5}$ from other pollutants, Gold et al. (1999) studied possible interactive effects of $PM_{2.5}$ and ozone on PEF; they found independent effects of the two pollutants, but the joint effect was slightly less than the sum of the independent effects.

The effects on respiratory symptoms in asthmatics also tended to be positive, although much less consistent than the lung function effects. Most studies showed increases in cough,

phlegm, difficulty breathing, and bronchodilator use (although generally not statistically significant), as shown in Figure 9-21 for cough as an example. Three studies included both PM_{10} and $PM_{2.5}$ in their analyses. The studies of Peters et al. (1997c) and Tiittanen et al. (1999) found comparable effects for the two measures. Only the Romieu et al. (1996) found slightly larger effects for $PM_{2.5}$. These studies also give no good evidence for a stronger effect of $PM_{2.5}$ when compared to PM_{10}.

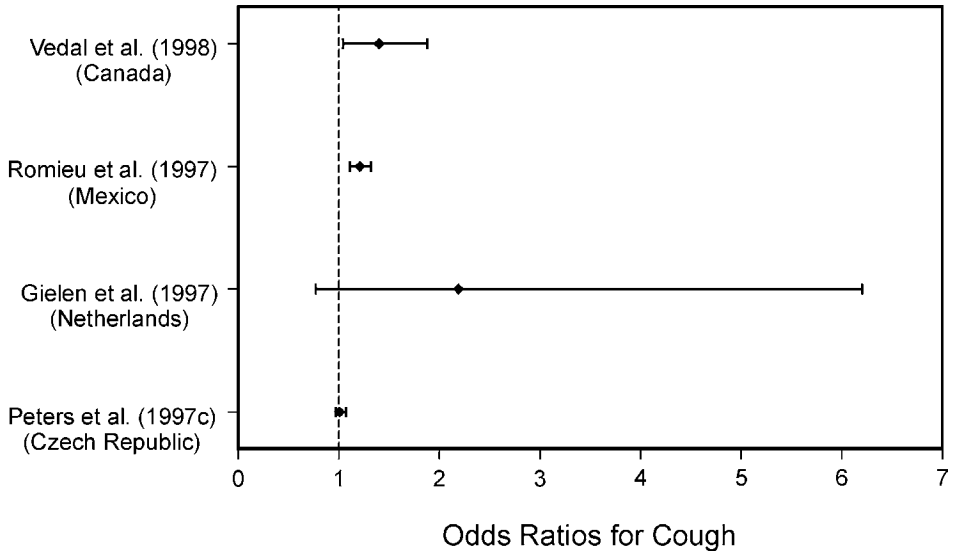

Figure 9-21. Odds ratios for cough for a 50-µg/m^3 increase in PM_{10} for selected asthmatic children studies, with lag 0 with 95% CI.

Two asthma studies, both in the United States, examined PM indicators by 1 hr averages as well as by 24 hr averages. The PM_{10} 1 hr outcome was larger than the 24 hr outcome for lower respiratory illness in one study (Delfino et al., 1998) but was lower for cough in the other study (Ostro et al., 2001). Several of the studies reviewed above (Delfino et al., 1998, 2002; Ostro et al., 2001; Yu et al., 2000; Mortimer et al., 2002; Vedal et al., 1998) that were conducted in the United States and Canada found positive associations between various health endpoints for asthmatics and ambient PM exposure (indexed by PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$). The endpoints

included PEF decrements, various individual respiratory symptoms, and combinations of respiratory symptoms. The various endpoints each represent effects on respiratory health.

The results of PM_{10} peak flow analyses for nonasthmatic populations were inconsistent. Fewer studies reported results in the same manner as the asthmatic studies. Many of the point estimates showed increases rather than decreases. $PM_{2.5}$ studies found similar results. The effects on respiratory symptoms in nonasthmatics were similar to those in asthmatics: most studies showed that PM_{10} increases cough, phlegm, and difficulty breathing, but these increases were generally not statistically significant. Schwartz and Neas (2000) found that $PM_{10-2.5}$ was significantly related to cough. Tiittanen et al. (1999) found that 1-day lag of $PM_{10-2.5}$ was related to morning PEF, but not evening PEF. Neas et al. (1999) found no association of $PM_{10-2.5}$ with PEF in non-asthmatic subjects.

The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle effects on healthy school children using two pollutant models of fine and coarse PM. Coarse PM was estimated by subtracting $PM_{2.1}$ from PM_{10} data. They report for cough (based on reanalysis of the Harvard Six City Diary Study in the two PM pollutant model) $PM_{2.5}$ OR = 1.07 (0.90, 1.26; per 15 $\mu g/m^3$ increment) and $PM_{10-2.5}$ OR 1.18 (1.04, 1.34; per 8 $\mu g/m^3$ increment) 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). In the Uniontown reanalysis, peak flow for $PM_{2.1}$ for a 14 $\mu g/m^3$ increment was −0.91 1/m (−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 (−1.13, +0.01) and $PM_{10-2.1}$ −0.17 (−2.07, +1.72).

9.8.2.1 Methodological Issues for Short-Term Exposure Studies

Chapter 8 discussed several still important methodological issues related to assessment of the overall PM epidemiologic database. These include, especially, issues related to model specifications and consequent adequacy of control for potentially confounding of PM effects by co-pollutants, evaluations of possible source relationships to pollutant effects that may be useful in better sorting out effects attributable to PM versus other co-pollutants or both, and other issues such as lag structure. Key points are discussed concisely below.

Time Series Studies: Confounding by Co-Pollutants in Individual Cities

The co-pollutant issue was discussed at length in the 1996 document and still remains an important issue. It must be recognized that there are large differences in concentrations of measured gaseous co-pollutants (and presumably unmeasured pollutants as well) in different parts of the United States, as well as the rest of the world; and the concentrations are often correlated with concentrations of PM and its components because of commonality in source emissions, wind speed and direction, atmospheric processes, and other human activities and meteorological conditions. Large sources in the United States include motor vehicle emissions (gasoline combustion, diesel fuel combustion, evaporation, particles generated by tire wear, etc.), coal combustion, fuel oil combustion, industrial processes, residential wood burning, solid waste combustion, and so on. Thus, one might reasonably expect some large correlations among PM and co-pollutants, but possibly with substantial differences in relation by season in different cities or regions. Statistical theory suggests that PM and co-pollutant effect size estimates will be highly unstable and often insignificant in multi-pollutant models when collinearity exists. Many recent studies demonstrate this effect, for both hospital admissions (Moolgavkar, 2000b) and mortality (Moolgavkar, 2000a; Chock et al., 2000). Because the problem seems largely insoluble in studies in single cities, the new multi-city studies (Samet et al., 2000a,b; Schwartz, 1999; Schwartz and Zanobetti, 2000) have provided important new insights. See discussions of NMMAPS analysis in Chapter 8 and below for discussion of issues related to control for co-pollutant effects. Overall, although such issues may warrant further evaluation, it now appears unlikely that such confounding accounts for the vast array of effects attributed to ambient PM based on the rapidly expanding PM epidemiology database.

Numerous new studies have reported associations not only between PM, but also gaseous pollutants (O_3, SO_2, NO_2, and CO), and mortality. In many of these studies, simultaneous inclusion of one or more gaseous pollutants in regression models did not markedly affect PM effect size estimates, as was generally the case in the NMMAPS analyses for 90 cities (see Figure 9-22). On the other hand, some studies reporting positive and statistically significant effects for gaseous co-pollutants (e.g., O_3, NO_2, SO_2, CO) found varying degrees of robustness of their effects estimates or those of PM in multi-pollutant models as discussed in Chapter 8 (Section 8.4). Thus, although it is likely that there are independent health effects of PM and gaseous pollutants, there is not yet sufficient evidence by which to confidently separate out fully

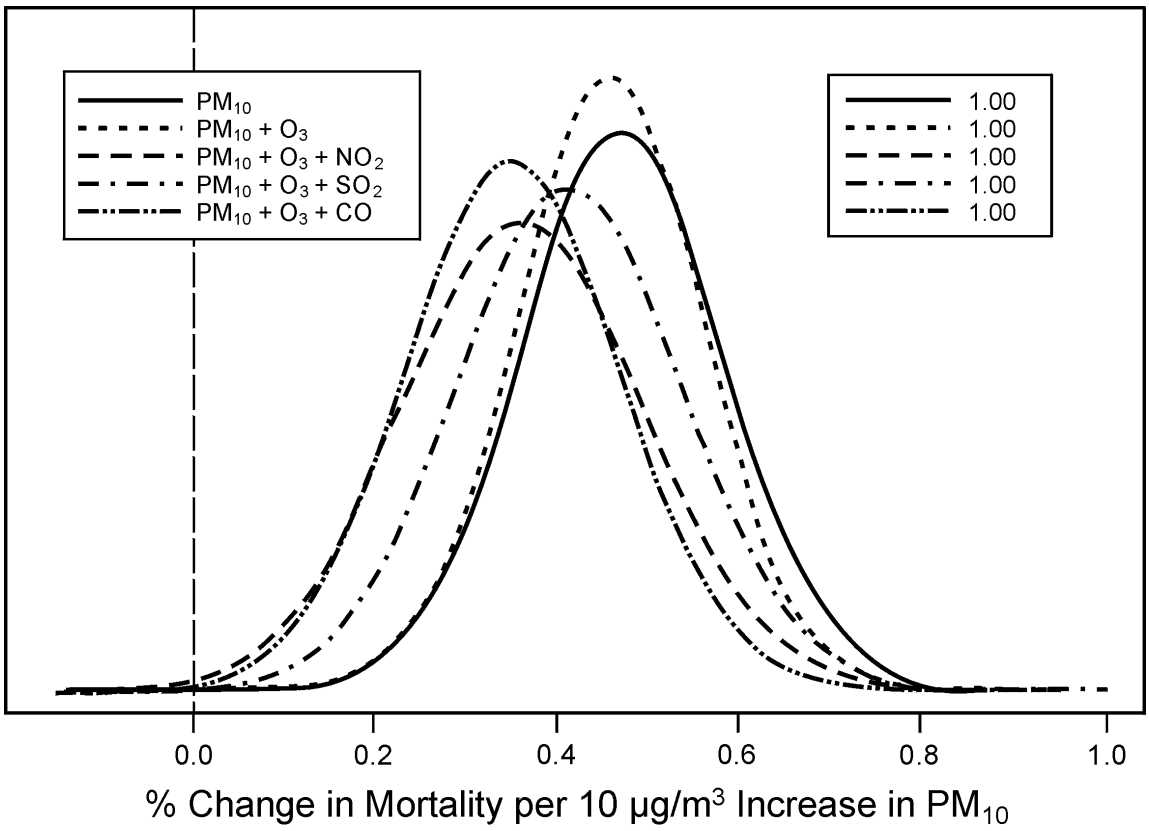

Figure 9-22. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1, with and without control for other pollutants, for the NMMAPS 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Dominici et al. (2003).

the relative contributions of PM versus those of other gaseous pollutants or by which to quantitate modifications of PM effects by other co-pollutants, including possible synergistic interactions that may vary seasonally or from location to location. Overall, it appears, however, that ambient PM and O_3 can be most clearly separated out as likely having independent effects, their concentrations often not being highly correlated. More difficulty is encountered, at times, in sorting out whether NO_2, CO, or SO_2 are exerting independent effects in cities where they tend to be highly correlated with ambient PM concentrations, possibly because of derivation of important PM constituents from the same source (e.g., NO_2, CO, and PM from mobile sources)

and/or a gaseous pollutant (e.g., SO_2) serving as a precursor for a significant PM component (e.g., sulfate).

Other information discussed in Section 8.4 on conceptual frameworks for evaluating possible confounding makes it clear that diagnostic evaluations of inflation or deflation of PM effect size estimates by addition of gaseous co-pollutants into multiple pollutant models, at best, may indicate potential confounding of PM effects in a given analysis. Other independently-derived exposure analyses, i.e., Sarnat et al. (2000, 2001), however, strongly suggest a very low probability of observed PM effects being due to confounding with gaseous criteria pollutants (CO, NO_2, SO_2, O_3) having high correlations with important PM constituents from the same source (e.g., NO_2, CO, and PM from mobile sources) or for gaseous pollutants (e.g., SO_2) serving as a precursor for a significant PM component (e.g., sulfate).

Time Series Studies: Model Selection for Lags, Moving Averages, and Distributed Lags

A number of different approaches have been used to evaluate the temporal dependence of mortality or morbidity on time-lagged PM concentrations, including unweighted moving averages of PM concentrations over one or more days, general weighted moving averages, and polynomial distributed moving averages. Unless there are nearly complete daily data, each different lag will be using a different set of mortality data corresponding to spaced PM measurement; for example, for lag 0 with every-sixth-day PM measurements, the mortality data are on the same day as the PM data, for lag 1 the mortality data are on the next day after the PM data, and so on. Although this effect is likely to be small, it should nonetheless be kept in mind.

The distributed lag models used in the NMMAPS II morbidity studies are a noteworthy methodological advance. The fitted distributed lag models showed significant heterogeneity across cities for COPD and pneumonia, however (see Table 15 therein), again raising the question of how heterogeneous effects can best be combined so as not to obscure potentially real city-specific or region-specific differences.

Only three cities with nearly complete daily PM_{10} data were used to evaluate more general multi-day lag models (Chicago, Minneapolis/St. Paul, Pittsburgh), and these show somewhat different patterns of effect, with lag 0 < lag 1 and lag 1 >> lag 2 for Chicago, lag 0 = lag 1 > lag 2 for Minneapolis, and lag 0 < lag 1 = lag 2 for Pittsburgh. The 7-day distributed lag model is

significant for Pittsburgh, but less so in the other cities. The remaining data are limited intrinsically in what they can reveal about temporal structure.

Time Series Studies: Model Selection for Concentration-Response Functions

Given the number of analyses that needed to be performed, it is not surprising that most of the NMMAPS studies focused on linear concentration-response models. More recent studies (Daniels et al., 2000) for the 20 largest U.S. cities have found posterior mean effects of 2 to 2.7% excess risk of total daily mortality per 50 $\mu g/m^3$ 24-h PM_{10} at lags 0, 1, 0+1 days; 2.4 to 3.5% excess risk of cardiovascular and respiratory mortality; and 1.2 to 1.7% for other causes of mortality. The posterior 95% credible regions are all significantly greater than 0. However, the threshold models gave distinctly different estimates of 95% credible regions for the threshold for total mortality (15 $\mu g/m^3$ at lag 1, range 10 to 20), cardiovascular and respiratory mortality (15 $\mu g/m^3$ at lag 0+1, range 0 to 20), and other causes of mortality (65 $\mu g/m^3$ at lag 0+1, range 50 to 75 $\mu g/m^3$).

Another problem is that the shape of the relationship between mortality and PM_{10} may depend, to some extent, on the associations of PM_{10} with gaseous co-pollutants. The association is not necessarily linear, and is indeed likely to have both seasonal and secular components that depend on the city location. Thus, further elaborations of these models is desirable.

Effects of Exposure Error in Daily Time Series Epidemiology

There has been considerable controversy over how to deal with the nonambient component of personal exposure. Recent biostatistical analyses of exposure error have indicated that the nonambient component will not bias the statistically calculated risk in community time-series epidemiology, provided that the nonambient component of personal exposure is independent of the ambient concentration. Consideration of the random nature of nonambient sources and recent studies, in which estimates of α, ambient-generated PM divided by ambient PM concentrations, have been used to estimate separately the ambient-generated and nonambient components of personal exposure, support the assumption that the nonambient exposure is independent of the ambient concentration. Therefore, it is reasonable to conclude that community time series epidemiology describes statistical associations between health effects and

exposure to ambient-generated PM, but does not provide any information on possible health effects resulting from exposure to nonambient PM (e.g., indoor-generated PM).

From the point of view of exposure error, it is also significant to note that, although ambient concentrations of a number of gaseous pollutants (O_3, NO_2, SO_2) often are found to be highly correlated with various PM parameters, personal exposures to these gases are not correlated highly with personal exposure to PM indicators. The correlations of the ambient concentrations of these gases also are not correlated highly with the personal exposure to these gases. Therefore, when significant statistical associations are found between these gases and health effects, it could be that these gases may, at times, be serving as surrogates for PM rather than being causal themselves. Pertinent information on CO has not been reported.

The attenuation factor, α, is a useful variable. For relatively constant α, the risk because of a personal exposure to 10 $\mu g/m^3$ of ambient PM is equal $1/\alpha$ times the risk from a concentration 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 health risk for an interquartile change in ambient concentration of PM is the same as that for an interquartile change in exposure to ambient PM). Differences in α among cities, reflecting differences in air-exchange rates (e.g., because of variation in seasonal temperatures and in extent of use of air conditioners) and differences in indoor/outdoor time ratios, may, in part, account for any differences in risk estimates based on statical associations between ambient concentrations and health effects for different cities or regions. If α were 0.3 in city A, but 0.6 in city B, and the risks for an increase in personal exposure of 10 $\mu g/m^3$ were identical, then a regression of health effects on ambient concentrations would yield a health risk for city B that would be twice that obtained for city A.

A number of exposure analysts have discussed the PM exposure paradox (i.e., that epidemiology yields statistically significant associations between ambient concentrations and health effects even though there is a near zero correlation between ambient concentrations and personal exposure in many studies). Several explanations have been advanced to resolve this paradox. First, personal exposure contains both an ambient-generated and a nonambient component. Community time series epidemiology yields information only on the ambient-generated component of exposure. Therefore, the appropriate correlation to investigate is the correlation between ambient concentration and personal exposure to ambient-generated PM, not between ambient concentrations and total personal exposure (i.e., the sum of ambient-generated

and nonambient PM). Second, biostatistical analysis of exposure error indicates that if the risk function is linear in the PM indicator, the average of the sum of the individual risks (risk function times individual exposure) may be replaced by the risk function times the community average exposure. Thus, the appropriate correlation (of ambient concentrations and ambient-generated exposure) is not the pooled correlation of different days and different people but the correlation between the daily ambient concentrations and the community average daily personal exposure to ambient-generated PM. Because the nonambient component is not a function of the ambient concentration, its average will tend to be similar each day. Therefore, the correlation coefficient will depend on α but not on the nonambient exposure. These types of correlation yield high correlation coefficients.

A few studies have conducted simulation analyses of effects of measurement errors on the estimated PM mortality effects. These studies suggest that ambient PM excess risk effects are more likely underestimated than overestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of the coefficient) because of transferring of effects from other covariates require extreme conditions and are therefore very unlikely. The error because the difference between the average personal exposure and the ambient concentration is likely the major source of bias in the estimated relative risk. One study also suggested that apparent linear exposure-response curves are unlikely to be artifacts of measurement error.

In conclusion, for time-series epidemiology, ambient concentration is a useful surrogate for personal exposure to ambient-generated PM, although the risk per unit ambient PM concentration is biased low by the factor α compared to the risk per unit exposure to ambient-generated PM. Epidemiologic studies of statistical associations between long-term effects and long term ambient concentrations compare health outcome rates across cities with different ambient concentrations. Ordinarily, PM exposure measurement errors are not expected to influence the interpretation of findings from either the community time-series or long-term epidemiologic studies that have used ambient concentration data if they include sufficient adjustments for seasonality and key personal and geographic confounders. When individual level health outcomes are measured in small cohorts, to reduce exposure misclassification errors, it is essential that better real-time exposure monitoring techniques be used and that further speciation of indoor-generated, ambient, and personal PM mass be accomplished. This should enable measurement (or estimation) of both ambient and nonambient components of personal

exposure and evaluation of the extent to which personal exposure to ambient-generated PM, personal exposure to nonambient PM, or total personal exposure (to ambient-generated plus nonambient PM) contribute to observed health effects.

9.8.3 Health Effects of Long-Term Exposures to Particulate Matter

The health effects of long-term ambient PM exposures have been epidemiologically studied in recent years mainly by prospective cohort studies that offer advantages over purely ecological analyses. Prospective cohort studies of ambient air pollutants are methodologically similar to typical epidemiologic 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). This 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.

Updated Epidemiologic Findings for Long-Term Particulate Matter Exposure Effects on Mortality

The 1996 PM AQCD indicated that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins (see appendix Table 9A-3). The PM effect size estimates for total mortality from these studies also indicated that a substantial portion of these deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events. Table 9-11 shows long-term exposure effects estimates (RR values) per variable increments in ambient PM indicators in U.S. and Canadian cities, including results from newer analyses since the 1996 PM AQCD.

TABLE 9-11. EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect Study and Location	Indicator	Change in Health Indicator per Increment in PM	Range of City PM Levels ** Means ($\mu g/m^3$)
Increased Total Mortality in Adults		**Relative Risk (95% CI)**	
Six City[A]	$PM_{15/10}$ (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[B] (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[C]	$PM_{15/10}$ (20 $\mu g/m^3$)	1.19 (1.06-1.34)	18.2-46.5
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.14 (1.05-1.23)	11.0-29.6
ACS Study Reanalysis[C]	$PM_{15/10}$ (20 $\mu g/m^3$) (dichot)	1.04 (1.01, 1.07)	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[D]	$PM_{2.5}$ (10 $\mu g/m^3$)	1.04 (1.01-1.08)	21.1 (SD=4.6)
Southern California[E]	PM_{10} (20 $\mu g/m^3$)	1.091 (0.985-1.212; males)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	1.082 (1.008-1.162; males)	
	PM_{10} (20 $\mu g/m^3$)	0.950 (0.873-1.033; females)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	0.958 (0.899-1.021; females)	
Veterans Cohort[F]	$PM_{2.5}$ (10 $\mu g/m^3$)	0.90 (0.85, 0.954; males)	5.6-42.3
Increased Cardiopulmonary Mortality in Adults		**Relative Risk (95% CI)**	
Six City[A]	$PM_{15/10}$ (20 $\mu g/m^3$)	***	18-47
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.18 (1.06, 1.32)	11-30
Six City Reanalysis[C]	$PM_{15/10}$ (20 $\mu g/m^3$)	1.20 (1.29, 1.41)	18.2-46.5
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.19 (1.07, 1.33)	11.0-29.6
ACS Study[B] (151 U.S. SMSA)	$PM_{2.5}$ (10 $\mu g/m^3$)	1.12 (1.07-1.17)	9-34
ACS Study Reanalysis[C]	$PM_{15/10}$ (20 $\mu g/m^3$) (dichot)	1.07 (1.03, 1.12)	58.7 (34-101)
	$PM_{2.5}$ (10 $\mu g/m^3$)	1.12 (1.07-1.17)	9.0-33.4
Southern California[E]	PM_{10} (20 $\mu g/m^3$)	1.01 (0.92, 1.10)	51 (±17)

TABLE 9-11 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect Study and Location	Indicator	Change in Health Indicator per Increment in PM	Range of City PM Levels ** Means ($\mu g/m^3$)
Increased Bronchitis in Children		**Odds Ratio (95% CI)**	
Six City[G]	$PM_{15/10}$ (50 $\mu g/m^3$)	3.26 (1.13, 10.28)	20-59
24 City[H]	$SO_4^=$ (15 $\mu g/m^3$)	3.02 (1.28, 7.03)	18.1-67.3
24 City[H]	$PM_{2.1}$ (10 $\mu g/m^3$)	1.31 (0.94, 1.84)	9.1-17.3
24 City[H]	PM_{10} (20 $\mu g/m^3$)	1.60 (0.92, 2.78)	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} (20 $\mu g/m^3$)	0.95 (0.79, 1.15)	28.0-84.9
12 Southern California communities[K] (children with asthma)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$)	1.4 (1.1, 1.8) 1.3 (0.9, 1.7)	13.0-70.7 6.7-31.5
Increased Cough in Children		**Odds Ratio (95% CI)**	
12 Southern California communities[J] (all children)	PM_{10} (20 $\mu g/m^3$)	1.05 (0.94, 1.16)	28.0-84.9
12 Southern California communities[K] (children with asthma)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$)	1.1 (0.7, 1.8) 1.2 (0.8, 1.8)	13.0-70.7 6.7-31.5
10 Canadian Communities[L]	PM_{10} (20$\mu g/m^3$)	1.19 (1.04, 1.35)	13-23
Increased Wheeze in Children		**Odds Ratio (95% CI)**	
10 Canadian Communities[M]	PM_{10} (20 $\mu g/m^3$)	1.35 (1.10, 1.64)	13-23
Increased Airway Obstruction in Adults		**Odds Ratio (95% CI)**	
Southern California[M]	PM_{10} (20 $\mu g/m^3$)	1.19 (0.84, 1.68)	NR
Decreased Lung Function in Children		**Odds Ratio (95% CI)**	
Six City[G]	$PM_{15/10}$ (50 $\mu g/m^3$)	NS Changes	20-59
24 City[N]	$PM_{2.1}$ (10 $\mu g/m^3$)	–2.15% (-3.34, -0.95) FVC	18.1-67.3
24 City[N]	$SO_4^=$ (7 $\mu g/m^3$)	–3.06% (-4.50, -1.60) FVC	9.1-17.3
24 City[N]	PM_{10} (20 $\mu g/m^3$)	–2.80% (-4.97, -0.59) FVC	22.0-28.6

TABLE 9-11 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect Study and Location	Indicator	Change in Health Indicator per Increment in PM	Range of City PM Levels ** Means ($\mu g/m^3$)
Decreased Lung Function in Children (cont'd)			
12 Southern California communities[O] (all children)	PM_{10} (20 $\mu g/m^3$)	−19.9 (-37.8, -2.6) FVC	28.0-84.9
12 Southern California communities[O] (all children)	PM_{10} (20 $\mu g/m^3$)	−25.6 (-47.1, -5.1) MMEF	28.0-84.9
12 Southern California communities[P] (4^{th} grade cohort)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$) $PM_{10-2.5}$ (10 $\mu g/m^3$)	−0.23 (-0.44, -0.01) FVC % growth −0.18 (-0.36, 0.0) FVC % growth −0.22 (-0.47, 0.02) FVC % growth	NR
12 Southern California communities[P] (4^{th} grade cohort)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$) $PM_{10-2.5}$ (10 $\mu g/m^3$)	−0.51 (-0.94, -0.08) MMEF % growth −0.4 (-0.75, -0.04) MMEF % growth −0.54 (-1.0, -0.06) MMEF % growth	NR
12 Southern California communities[Q] (4^{th} grade cohort follow-up)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$)	−0.23 (-0.46, -0.0) FVC % growth −0.19 (-0.39, 0.01) FVC % growth	NR
12 Southern California communities[Q] (4^{th} grade cohort follow-up)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$)	−0.55 (-1.0, -0.08) MMEF % growth −0.42 (-0.85, 0.01) MMEF % growth	NR
12 Southern California communities[Q] (4^{th} grade cohort follow-up)	PM_{10} (20 $\mu g/m^3$) $PM_{2.5}$ (10 $\mu g/m^3$)	−0.49 (-0.84, -0.14) PEFR % growth −0.37 (-0.70, -0.04) PEFR % growth	NR
Southern California[R]	PM_{10} (20 $\mu g/m^3$)	-3.6 (-18, 11) FVC growth	15.0-66.2
Southern California[R]	PM_{10} (20 $\mu g/m^3$)	-33 (-64, -2.2) MMEF growth	15.0-66.2
Southern California[R]	PM_{10} (20 $\mu g/m^3$)	-70 (-120, -20) PEFR growth	15.0-66.2
Lung Function Changes in Adults		**Odds Ratio (95% CI)**	
Southern California[S] (% 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[S] (% 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[S] (% 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)

TABLE 9-11 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect Study and Location	Indicator	Change in Health Indicator per Increment in PM	Range of City PM Levels ** Means ($\mu g/m^3$)
Lung Function Changes in Adults (cont'd)			
Southern California[S] (% 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)

* 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.

** Range of mean PM levels given unless, as indicated, studies reported overall study mean (min, max), or mean (±SD); NR=not reported.

*** Results only for smoking category subgroups.

References:

[A]Dockery et al. (1993)
[B]Pope et al. (1995)
[C]Krewski et al. (2000)
[D]Pope et al. (2002)
[E]Abbey et al. (1999)
[F]Lipfert et al. (2000b)
[H]Dockery et al. (1989)
[H]Dockery et al. (1996)
[I]Abbey et al. (1995a,b,c)
[J]Peters et al. (1999b)
[K]McConnell et al. (1999)
[L]Howel et al. (2001)
[M]Berglund et al. (1999)
[N]Raizenne et al. (1996)
[O]Peters et al. (1999c)
[P]Gauderman et al. (2000)
[Q]Gauderman et al. (2002)
[R]Avol et al. (2001)
[S]Abbey et al. (1998)

Several advances have been made in terms of further analyses and/or reanalyses of several studies of long-term PM exposure effects on total, cardiopulmonary, or lung cancer mortality. These include reanalyses by Krewski et al. (2000) of the Harvard Six-Cities Study originally reported by Dockery et al. (1993); reanalyses by Krewski et al. (2000) of America Cancer Society (ACS) Study data and analyses originally reported on by Pope et al. (1995); extended analyses of ACS data covering 16 more years of follow-up (Pope et al., 2000), new analysis of extended years of data from the Adventist Health Study of SMOG (AHSMOG) reported by Abbey et al. (1999) and McConnell et al. (2000); for Southern California residents; and a newly available Veterans Administration (VA) study of U.S. veterans published by Lipfert et al. (2000b). Table 9-11 includes key results (excess relative risks for total, cardiopulmonary, and lung cancer mortality associated with long-term ambient PM exposure) from these studies.

Two of these survival studies were national in scope, the Harvard Six-Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995), and

one focused solely on California, the Adventist Health Study of Smog or AHSMOG (Abbey et al., 1991). The ACS 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 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 AHSMOG Study 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 VA cohort study (Lipfert et al., 2000b) enrolled ~70,000 veterans who, at the time of enrollment, had high blood pressure and followed them health-wise for twenty years. Air quality data for their place of residence at time of enrollment was tracked from time periods prior to and during the study and related to mortality events.

One of the most important advances since the 1996 PM AQCD is the substantial verification and extension of the findings of the Harvard Six City prospective cohort study (Dockery et al., 1993) and the cohort study relating American Cancer Society (ACS) health data to fine-particle data from 50 cities and sulfate data from 151 cities (Pope et al., 1995). The reanalyses, sponsored by the Health Effects Institute (HEI), included a data audit, replication of the original investigators' findings, and additional analyses to explore the sensitivity of the original findings to other model specifications. The investigators of the HEI Reanalysis Project (Krewski et al., 2000) first performed a data audit, using random samples to verify the accuracy of the data sets used in the original Six City analyses, including death certificate data, air pollution data, and socioeconomic data. In general, the air pollution data were reproducible and correlated highly with the original aerometric data in Pope et al. (1995).

The reanalyses substantially verified the findings of the original investigators, with $PM_{2.5}$ or sulfate relative risk (RR) estimates for total mortality and for cardiopulmonary mortality differing at most by ±0.02 (±2% excess risk) from the least polluted to the most polluted cities in the study. A larger difference was noted for the $PM_{2.5}$ lung cancer relative risk in the Six Cities study, 1.37 originally and 1.43 in the reanalysis, neither estimate being statistically significant. The sensitivity analyses for the Six Cities study found generally similar results with other individual covariates included. The time-dependent covariate model for total mortality (taking

into account higher postexposures in early years of the study and changes over time to the last years of the study) had a substantially lower RR than the model without time-dependent covariates. Educational level made a large difference, with individuals having less than a high school education at much greater risk for mortality than those with any postsecondary education.

Among the ecological covariates, sulfates adjusted for artifact had little effect on the risk estimates for total mortality compared to that without adjustment, but, in the ACS study, the filter adjustment actually increased the relative risk for all causes and cardiopulmonary mortality, while substantially reducing the estimated sulfate effect on lung cancer. Inclusion of SO_2 as an additional ecological covariate greatly reduced the estimated $PM_{2.5}$ and sulfate effects in the ACS study, whereas a spatial model including SO_2 effects caused only a modest reduction of the estimated $PM_{2.5}$ and sulfate effects. However, the SO_2 effects were reduced greatly when sulfates were included in the model. Sulfur dioxide and sulfates often are highly correlated, because of the formation of secondary sulfates.

Many model selection issues in the prospective cohort studies are analogous to those in the time series analyses. One issue of particular concern is whether the exposure indices used in the analyses adequately characterize the exposure of the participants in the study during the months or years preceding death. This question is particularly conspicuous in regard to the Pope et al. (1995) study, in which $PM_{2.5}$ and sulfate data were collected in the 1979 to 1982 period from the EPA AIRS database and the Inhalable Particle Network, largely preceding the collection of the ACS cohort data by only a few years, and so possibly not adequately reflecting exposure to presumably much higher PM concentrations occurring long before the cohort was recruited, nor exposure to presumably lower concentrations during the study. This issue was raised in the 1996 PM AQCD. However, the Six Cities Study did have air pollution data and repeated survey data over time, with $PM_{2.5}$ and sulfate data measured every other day and sometimes daily, and so the new investigators were able to use the information about time-dependent cumulative PM concentrations during the course of the study. Changes in smoking status and body mass index over the 10 to12 years of the study had little effect on risk estimates, but taking into account the decrease in particle concentrations from the earlier years to the later years reduced the effect size estimate substantially, although it remained statistically significant. Nevertheless, overall, the reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) “replicated the original results, and tested those results against alternative risk models and analytic approaches

without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

The shape of the relationship of concentration to mortality also was explored. Preliminary findings suggest some possible nonlinearity, but further study is needed. Among the most important new findings of the study are spatial relationships between mortality and air pollution, discussed later below.

Recently reported extension of the ACS analyses (Pope et al., 2002) to include additional years of data provides further substantiation of originally reported findings for total, respiratory, and cardiovascular mortality. Also of great importance, these new analyses provide much stronger evidence substantiating links between long-term ambient fine PM exposures and lung cancer. This is consistent with findings of increased lung cancer risk being associated with exposure with diesel exhaust particles, an important constituent of $PM_{2.5}$ in many U.S. urban areas.

With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies generally have found that the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with chronic PM exposure-mortality. Although the relative measurement errors of the various PM constituents must be further evaluated as a possible source of bias in these estimate comparisons, the Harvard Six-Cities study and the latest reported AHSMOG prospective semi-individual study results (Abbey, et al., 1999; McDonnell et al., 2000) are both indicative of the fine mass components of PM likely being associated more strongly with the mortality effects of PM than coarse PM components. The ACS study, its reanalyses, and its recent extension all further substantiate ambient fine particle effects, including increased risk not only of cardiopulmonary-related mortality but lung cancer mortality as well.

The Harvard Six Cities analyses (as confirmed by the HEI reanalyses) and the recent extension of the ACS study by Pope et al. (2002) probably provide the most credible and precise estimates of excess mortality risk associated with long-term PM exposures in the United States. Of particular interest are their statistically significant effects estimates for $PM_{2.5}$, falling in a range of 4.0 to 14.0% total mortality per 10 $\mu g/m^3$ annual average increment ,and the 10-46% excess risk per 15 $\mu g/m^3$ increase in long-term sulfate concentrations.

Several other new studies report epidemiologic evidence indicating that: (a) PM exposure early in pregnancy (during the first month) may be associated with slowed intrauterine growth leading to low birth weight events (Dejmek et al., 1999); and (b) early postnatal PM exposures may lead to increased infant mortality (Woodruff et al., 1997; Boback and Leon, 1999; Loomis et al., 1999; Lipfert et al., 2000b).

Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a similar type of questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a chronic PM exposure effect on respiratory disease. The analysis of chronic cough, chest illness, and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with highest exposure of strongly acidic particles when compared with the least polluted community. Fine ZPM sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

The studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) all had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect on children of PM pollution indexed by TSP, PM_{15}, $PM_{2.5}$, or sulfates. In contrast, the later 24-city analyses reported by Raizenne et al. (1996) found significant associations of effects on FEV_1 or FVC in U.S. and Canadian children with both acidic particles and other PM indicators. Overall, the available studies provided limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.).

A number of studies have been published since 1996 which evaluate the effects of long-term PM exposure on lung function and respiratory symptoms, as presented in Chapter 8. The methodology in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to PM), whereas others

reported no significant results. Of particular note are several studies reporting associations between long-term PM exposures (indexed by various measures) or changes in such exposures over time and chronic bronchitis rates, consistent with the findings on bronchitis from the Dockery et al. (1996) study noted above.

Unfortunately, the cross-sectional studies often are potentially confounded, in part, by unexplained differences in geographic regions; and it is difficult to separate out results consistent with a PM gradient from any other pollutants or factors having the same gradient. The studies that looked for a time trend also are confounded by other conditions that changed over time. The most credible cross-sectional study remains that described by Dockery et al. (1996) and Raizenne et al. (1996). Whereas most studies include two to six communities, this study included 24 communities and is considered to provide the most credible estimates of long-term PM exposure effects on lung function and respiratory symptoms.

Thus, the relative risk estimates for these three survival cohorts have converged in the range of 7 to 13 percent increase in the non-external mortality rate associated with a 10 $\mu g/m^3$ increment in a long-term average of $PM_{2.5}$. Methodological criticisms of these studies have been largely resolved in favor of the validity of their original findings of a strong association between long-term exposures to particulate matter and decreased survival (Bates, 2000).

9.8.4 Coherence of Reported Epidemiologic Findings

Interrelationships Between Health Endpoints. Considerable coherence exists across newly available epidemiologic study findings. For example, it was earlier noted that effects estimates for total (nonaccidental) mortality generally fall in the range of 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ 24-h PM_{10} increment. These estimates comport well with those found for cause-specific cardiovascular- and respiratory-related mortality.

Furthermore, larger effect sizes for cardiovascular (in the range of 3 to 6% per 25 $\mu g/m^3$ 24-h PM_{10} increment) and respiratory (in the range of 5 to 25% per 25 $\mu g/m^3$ 24-h PM_{10}) hospital admissions and visits are found, as would be expected versus those for PM_{10}-related mortality. Also, several independent panel studies, evaluating temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects, provide generally consistent indications of decreased heart rate (HR) variability being associated with ambient PM exposure (decreased HR variability being an indicator of increased risk for serious cardiovascular outcomes, e.g., heart

attacks). Other studies point toward changes in blood characteristics (e.g., increased C-reactive protein levels) related to increased risk of ischemic heart disease as also being associated with ambient PM exposures. In addition, new evidence exists for ambient PM associations with reductions in pulmonary function and/or increased respiratory symptoms, especially of note in relation to asthmatic or other chronic lung disease individuals. All these CVD and respiratory morbidity effects add to the coherence of the overall evidence substantiating short-term PM exposure effects on susceptible population groups.

The overall body of controlled human and/or laboratory animal exposure studies discussed earlier also add coherence to the evidence for ambient PM-related health impacts. A number provide evidence that supports one or another hypothesis with regard to (a) PM components (by size, chemical composition, etc.) and/or (b) mechanisms likely contributing to PM effects on various cardiovascular or respiratory endpoints. The results of instillation studies, using filter extracts from community monitoring stations in the Utah Valley before, during, and after temporary shut down of a steel mill there are particularly compelling on two accounts: (1) the evidence of greater lung inflammation from instilled extracts from periods of mill operation parallel epidemiologic findings of increased cardiorespiratory hospitalizations during such periods; and (2) dosimetric calculations indicate that concentrations of particulate extract materials likely delivered to affected lung tissue with the instillation would probably be reasonably comparable to those likely experienced in connection with inhalation exposures to PM_{10} concentrations in the Utah Valley PM mixture.

Spatial Interrelationships. Both the NMMAPS and Cohort Reanalyses studies had a sufficiently large number of cities to allow considerable resolution of regional PM effects within the “lower 48" states, but this approach was taken much farther in the Cohort Reanalysis studies than in NMMAPS. There were 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in Pope et al. (1995) and in the reanalyses using the original data; and, in the additional analyses by the cohort study reanalysis team, 63 cities with $PM_{2.5}$ data and 144 cities with sulfate data. The relatively large number of data points allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers. Information drawn from the maps presented in Figures 16-21 in Krewski et al. (2000) is summarized below.

The patterns are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski, Figure 18) has peak levels in the industrial midwest, including the Chicago and Cleveland areas, the upper Ohio River Valley, and around Birmingham, AL. Lower, but elevated, $PM_{2.5}$ is found almost everywhere else east of the Mississippi, as well as in southern California. This was rather similar to the modeled sulfate surface (Krewski, Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only region with elevated SO_2 concentrations was the Cleveland-Pittsburgh area. A preliminary evaluation is that secondary sulfates in particles derived from local SO_2 were more likely to be important in the industrial midwest, south from the Chicago-Gary region and along the upper Ohio River region.

The overlay of mortality and air pollution is also of interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewksi, Figure 21) was highest for the upper Ohio River region, but also includes a significant association over most of the industrial midwest. This was reflected, in diminished form, by the sulfates map (Krewski, Figure 19) where the peak sulfate-mortality associations occur somewhat east of the peak $PM_{2.5}$-mortality associations. The SO_2 map (Krewski, Figure 20) shows peak associations similar to, but slightly east of, the peak sulfate associations. This suggests that, although SO_2 may be an important precursor of sulfates in this region, there may be other considerations (e.g., metals) in the association between $PM_{2.5}$ and long-term mortality, embracing a wide area of the midwest and northeast (especially noncoastal areas).

9.9 SUSCEPTIBLE SUBPOPULATIONS AND IMPLICATIONS OF EFFECTS OF AMBIENT PM EXPOSURE ON HUMAN HEALTH

9.9.1 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.

9.9.2 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.

9.9.2.1 Ambient PM Exacerbation of Cardiovascular Disease Conditions

Exacerbation of cardiovascular disease (CVD) has been associated epidemiologically, not only with ambient PM, but also with other combustion-related ambient pollutants such as CO. Thus, while leaving little doubt that ambient PM exposures importantly affect CVD mortality and morbidity, the quantitation of the proportion of risk for such exacerbation specifically attributable to ambient PM exposure is difficult. Recent studies (e.g., concentrated ambient particle studies [CAPS]) have demonstrated cardiovascular effects in response to ambient particle exposures, and studies utilizing animals and other approaches also have produced results suggesting plausible mechanisms leading to cardiovascular effects. However, much remains to be resolved with regard to delineation of dose-response relationships for the induction and

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)

	Age					Regional			
Chronic Condition/Disease	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).

DRAFT-DO NOT QUOTE OR CITE

extrapolation of such effects to estimate appropriate and effective human equivalent PM (or specific constituent/s) exposures.

The recent appreciation for underlying cardiovascular dysfunction as a risk factor for PM health effects derives from a growing and diverse body of literature. While many time-series studies have revealed stronger associations between PM exposures and mortality when a subpopulation was segregated for pre-existent cardiac disease, no direct and plausible evidence had previously been available. However, recent panel studies of human subjects with CVD (Peters et al., 2000) have shown correlations between air pollution levels, notably PM, and intervention discharge frequency of implanted cardiac defribrillators. Analogously, Pope and colleagues (2001) have noted altered autonomic control of cardiac electrocardiograms (in terms of heart rate variability) over a wide age- range of ostensibly healthy subjects when they were introduced into a room with active smokers. Evidence of vascular narrowing with exposure to concentrated ambient PM (CAPS) has likewise been reported suggesting parallel cardiovascular responses (Brook et al., 2002). Collectively, these and previous studies that have shown ambient PM-induced alterations in cardiac physiology (Pope et al, 1999a,b; Liao et al., 1999; Peters et al., 1999; Gold et al., 2000) in human subjects, complemented with animal studies (Godleski et al., 1996; Watkinson et al., 1998, 2001; Kodavanti et al., 2000), reinforce the notion of significant cardiac responses to PM. Moreover, indications of changes in plasma viscosity (Peters et al., 1997a) and other factors involved in clotting function (Ghio et al., 2000) provide a plausible cascade of events that could culminate in a sudden cardiac event in some individuals.

To the extent that the observed associations between ambient PM and heart disease exacerbation are causal and specific, the impact on public health could be dramatic. In 1997, there were about 4,188,000 U.S. hospital discharges with heart disease as the first-listed diagnosis (Lawrence and Hall, 1999). Among these, about 2,090,000 (50%) were for ischemic heart disease, 756,000 (18%) for myocardial infarction or heart attack (a subcategory of ischemic heart disease), 957,000 (23%) for congestive heart failure, and 635,000 (15%) for cardiac dysrhythmias. Also, there were 726,974 deaths from heart disease (Hoyert et al., 1999). Thus, even a small percentage reduction in PM-associated admissions or deaths from heart disease would predict a large number of avoided cases.

9.9.2.2 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 be a strong likelihood that infections may be worsened by exposure to PM, general statements regarding interaction of PM with response to

infectious agents are difficult given the unique attributes of various infectious agents and the immune status of the host.

The underlying biology of lung diseases might also lead to heightened sensitivity to PM (apart from the dose issue noted above), but this attribute of disease remains hypothetical in the context of PM. The functional linkages with the cardiac system for maintenance of adequate gas exchange and fluid balance notwithstanding, the role of inflammation in the diseased respiratory tract (airways and alveoli) could play a key role. Studies in animals genetically or exogenously altered to induce inflammation are sometimes intrinsically more responsive to surrogate or concentrated ambient PM. While a PM-induced response may on the one hand be cumulative with the underlying injury or condition, the responses may, on the other hand, be magnified by any number of mechanisms that are poorly understood. There is sufficient basic biological data to hypothesize that the exudated fluids in the airspaces may either interact differently with deposited PM (e.g., to generate oxidants - Costa and Dreher, 1999; Ghio et al., 2001) to augment injury, or predispose the lung (e.g., sensitize receptors - Undem and Carr, 2002) to enhance the response to a stereotypic PM stimulus through otherwise normal pathways. Less appreciated is the loss of reserve - functional or biochemical - where the susceptible individual is incapable of sufficient compensation (e.g., antioxidant responses - Kodavanti et al., 2000). Any of these or related mechanisms may contribute to "susceptibility" and may indeed be a common factor that can be attributable to other susceptible groups. Understanding these will ultimately aid in addressing true risk of susceptible groups to PM.

Again, even a small percentage reduction in PM health impacts on respiratory-related diseases could calculate out to a large number of avoided cases. In 1997, there were 3,475,000 U.S. hospital discharges for respiratory diseases: 38% for pneumonia, 14% for asthma, 13% for chronic bronchitis, 8% for acute bronchitis, and the remainder not specified (Lawrence and Hall, 1999). Of the 195,943 deaths recorded as caused by respiratory diseases, 44% resulted from acute infections, 10% from emphysema and bronchitis, 2.8% from asthma, and 42% from unspecified COPD (Hoyert et al., 1999).

9.9.3 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, mortality 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).

displayed graphically in Figure 9-23. The amount of air inhaled per kilogram body weight decreases dramatically with increasing age, due in part to ventilation differences (in cubic meters per kilogram a day) of a 10-year-old being roughly twice that of a 30-year-old person, even without the consideration of activity level. Child-adult dosage disparities are even greater when viewed on a per lung surface-area basis.

As to potential lung developmental impacts of PM, there exist both experimental and epidemiologic data, which although limited, suggest that the early post-neonatal period of lung development is a time of high susceptibility for lung damage by environmental toxicants. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000); and acute injury to the lung during early postnatal development may impair normal repair processes, such as down-regulation of cellular proliferation (Smiley-Jewel et al., 2000, Fanucchi et al., 2000). These results in animals appear concordant with recent findings for young children growing in the Los Angeles area where both oxidants and high PM prevail (Gauderman et al., 2000).

These and other types of health effects in children are emerging as potentially more important than appreciated in the 1996 PM AQCD. Unfortunately, relatively little is known

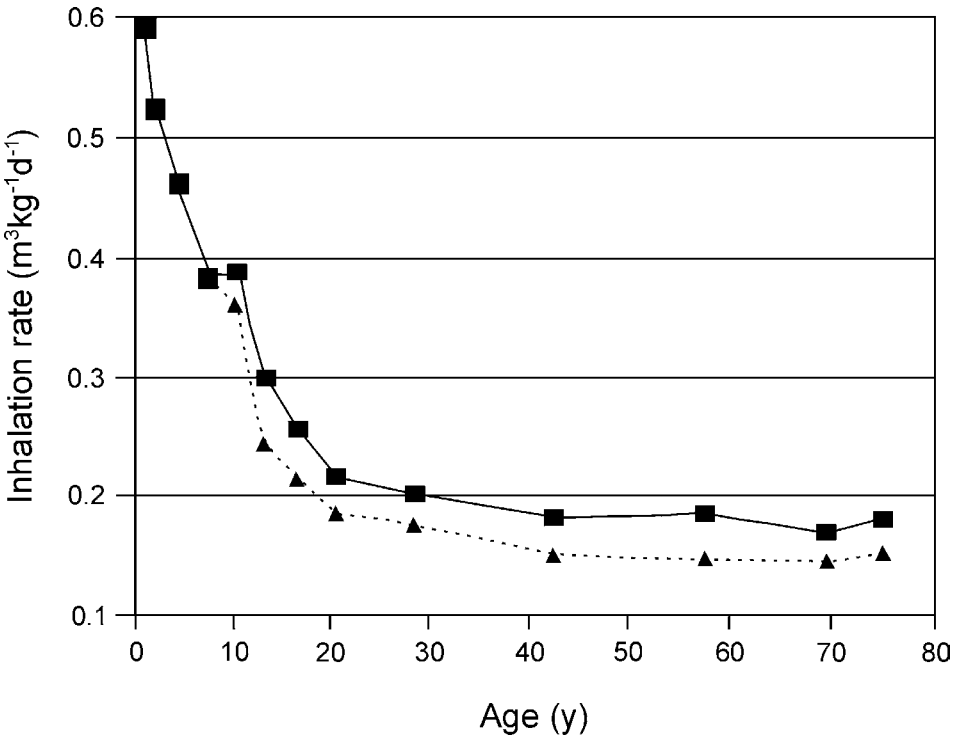

Figure 9-23. Inhalation rates on a per body-weight basis for males (■) and females (▲) by age (Layton, 1993).

about the relationship of PM to these and other serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in older children). The recent report by Ritz et al. (2002) linking CO exposures of mothers in Los Angeles with fetal cardiac defects raises concerns for PM, which was inconclusively linked in the study. Similarly, little is yet known about the involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. Thus, the loss of productive life-years that add to the costs to society may be more than just those indexed by PM-related mortality and/or hospital admissions/visits.

In summary, host variability may come to be the most important factor in determining the response profile of any population exposed to PM. Studies to date suggest that certain subpopulations are indeed more acutely responsive to PM, perhaps due to differences in lung deposition (either in terms of dose and/or intrapulmonary distribution) or other biologic aspects

of the cardiopulmonary system or disease thereof. The role of innate attributes of risk grounded in one's genetic code is largely unknown but potentially of great importance. Animal models have been used to show clear differences in response to PM and other pollutants, and the critical involvement of varied genes in the induction of asthma, emphysema, and many other ailments is widely accepted, but poorly understood.

9.9.4 Impact on Life-Expectancy

The increased rate of non-external mortality found in the three prospective cohort studies (Harvard Six Cities; ACC, AHSMOG) is greater than the mere accumulation of the adverse effects of short-term exposures for a few days. Conceptually, ambient PM exposures may be associated with both the long-term development of underlying health problems ("frailty") and with the short-term variations in timing of mortality among a susceptible population with some underlying health condition (Kunzli et al. 2001). Epidemiologic studies of the mortality effects of short-term exposure to particulate matter using time-series studies can only capture PM's association with short-term variations in mortality and, therefore, must systematically underestimate the proportion of total mortality attributable to PM. A recent time-series study that examined the contribution of daily PM levels over an extended lag period (42 days) could only partially bridge the gap between the effects of short-term and long-term exposures to particulate matter (Zanobetti et al., 2002).

Recent investigations of the public health implications of effect estimates for long-term PM exposures also were reviewed in Chapter 8. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to ambient airborne PM can have substantial effects on life expectancy. For example, a calculation for the 1969 to 1971 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of ~ 1.3 years for the entire population's life expectancy at age 25. The new evidence noted above of infant mortality associations with PM exposure suggests that life shortening in the entire population from long-term PM exposure could well be significantly larger than estimated by Brunekreef (1997).

The increase in non-external mortality cannot be explained by increases in chronic respiratory diseases since chronic non-malignant lower respiratory disease accounts for only 5.6 percent and lung cancer for only another 6.9 percent of all deaths over age 24 years due to

non-external causes. Cardiovascular diseases, which account for 43 percent of non-external mortality, must play the leading role in the decreased survival associated with exposure to ambient PM. It is nevertheless useful to highlight the newer results of the extension of the ACS study analyses (that include more years of participant follow-up and address previous criticisms of the earlier ACS analyses), which provide the strongest evidence to date that long-term ambient PM exposures are associated with increased risk of lung cancer. That increased risk appears to be in about the same range as that seen for a non-smoker residing with a smoker and, therefore, passively exposed chronically to tobacco smoke, with any consequent life-shortening impacts due to lung cancer.

9.10 INTEGRATIVE SYNTHESIS OF KEY FINDINGS FOR ENVIRONMENTAL EFFECTS OF AMBIENT AIRBORNE PM

9.10.1 Introduction

The 1997 EPA revisions to the U.S. PM NAAQS, discussed in Chapter 1 (Introduction), included establishment of $PM_{2.5}$ secondary standards identical to the primary $PM_{2.5}$ NAAQS set at that time. The 1997 FR notice promulgating these standards noted "The new secondary standards, in conjunction with a regional haze program, will provide appropriate protection against PM-related public welfare effects including soiling, material damage, and visibility impairment." This section of Chapter 9 concisely highlights salient information expected to provide inputs to EPA decision making on secondary National Ambient Air Quality Standards (NAAQS) aimed at protecting against welfare effects of ambient airborne particulate matter (PM). More specifically, it discusses effects of atmospheric PM on the environment, including: (a) direct and indirect effects on vegetation and natural ecosystem integrity; (b) effects on visibility; and (c) effects on man-made materials, as well as (d) relationships of atmospheric PM to climate change processes.

9.10.2 Effects of Ambient Airborne PM on Vegetation and Natural Ecosystems

The effects of airborne particles are manifested via direct physical and chemical effects exerted at the individual plant level and/or indirectly via deposition on soils and/or waterways.

However, plants are key members of ecosystems, structurally complex communities comprised of populations of plants, animals (including humans), insects, and microorganisms that interact with one another and with their non-living (abiotic) chemical and physical environment in which they exist (Odum, 1989; U.S. Environmental Protection Agency, 1993). All life on Earth is dependent on chemical energy in the form of carbon compounds to sustain their life processes. Terrestrial vegetation, via the process of photosynthesis, provides approximately half of the carbon that annually cycles between the Earth and the atmosphere (Chapin and Ruess, 2001).

Ecosystems respond to stresses through their constituent organisms. The responses of plant species and populations to environmental perturbations (such as those caused by atmospheric PM) depend on their genetic constitution (genotype), their life cycles, and the microhabitats in which they are growing. Stresses that produce changes in their physical and chemical environment apply selection pressures on individual organisms (Treshow, 1980). The changes that occur within populations and plant communities reflect these new and different pressures. A common response in a community under stress is the elimination of the more sensitive populations and an increase in abundance of species that tolerate or are favored by stress (Woodwell, 1970, Guderian et al., 1985).

The present section is organized to discuss: (1) factors affecting deposition of airborne PM on plants and ecosystems and then (2) the effects of PM deposition on individual plants, plant populations, forest trees, and terrestrial and aquatic ecosystems. As such, the section is organized to follow, in rough outline, the Framework for Assessing and Reporting on Ecological Condition recommended in a report by the Ecological Processes and Effects Committee (EPEC) of EPA's Science Advisory Board (Science Advisory Board, 2002), which states "The purpose of this report is to provide the Agency with a sample framework that may serve as a guide for designing a system to assess, and then report on, ecological condition at local, regional, or national scale. The sample framework is intended as an organizing tool that may help the Agency decide what ecological attributes to measure and how to aggregate those measurements into an understandable picture of ecological integrity." This framework is not actually a risk assessment per se, but it can be used to "construct a report of ecological condition" that characterizes the ecological integrity of an ecosystem based on "the relationship between common anthropogenic stressors and one or more of the six Essential Ecological Attributes."

It nevertheless does provide a useful approach for organizing discussions of stressor effects on ecosystem components at successive levels of complexity.

9.10.2.1 Ecological Attributes

The EPEC Framework provides a checklist of generic ecological attributes that should be considered when evaluating the integrity of ecological systems (see Table 9-14). The six generic ecological attributes, termed Essential Ecological Attributes (EEA), represent groups of related ecological characteristics (Science Advisory Board, 2002; Harwell et al., 1999) and include: Chemical and Physical Characteristics; Biotic Conditions; Landscape Conditions; Ecological Processes; Hydrology and Geomorphology; and Natural Disturbance Regimes. All of the EEAs are interrelated (i.e., changes in one EEA may directly or indirectly affect other EEAs).

The first three ecological attributes listed in Table 9-14 are primarily "patterns," whereas the last three are "processes." Ecological science has used "patterns" and "processes" as terms to describe features of ecological systems for many years (e.g., Bormann and Likens, 1979).

Of main concern in this chapter are relationships between a certain class of diverse airborne stressors from anthropogenic sources, termed particulate matter (PM), and one or more of the EEAs. Changes in patterns resulting from responses of vegetation and ecosystems to the effects of fine and coarse PM deposition, along with known or possible effects on ecological processes associated with changes in the patterns, are discussed in the subsections that follow.

The reader is also referred to several other sources for more detailed discussions of several topics only briefly alluded to or addressed here. For example, an extensive discussion of various types of effects of acidic deposition is presented in the U.S. National Acid Precipitation Assessment Program (NAPAP) Biennial Report to Congress: An Integrated Assessment Program (National Scientific and Technology Council, 1998). Additionally, ecological effects of acidic precipitation and nitrate deposition on aquatic systems are discussed in the EPA Air Quality Criteria Document for Nitrogen Oxides (U.S. Environmental Protection Agency, 1993); and sulfate deposition and effects, as related to wetlands and aquatic habitats, are discussed in U.S. Environmental Protection Agency (1982). Effects of lead on crops, vegetation, and ecosystems are assessed in the EPA document, Air Quality Criteria for Lead (U.S. Environmental Protection Agency, 1986). Lastly, effects of "certain pesticides, metal compounds, chlorinated organic compounds, and nitrogen compounds" are discussed in

TABLE 9-14. ESSENTIAL ECOLOGICAL ATTRIBUTES AND REPORTING CATEGORIES

Landscape Condition
- Extent of Ecological System/Habitat Types
- Landscape Composition
- Landscape Pattern and Structure

Biotic Condition
- Ecosystems and Communities
  - Community Extent
  - Community Composition
  - Trophic Structure
  - Community Dynamics
  - Physical Structure
- Species and Populations
  - Population Size
  - Genetic Diversity
  - Population Structure
  - Population Dynamics
  - Habitat Suitability
- Organism Condition
  - Physiological Status
  - Symptoms of Disease or Trauma
  - Signs of Disease

Chemical and Physical Characteristics (Water, Air, Soil, and Sediment)
- Nutrient Concentrations
  - Nitrogen
  - Phosphorus
  - Other Nutrients
- Trace Inorganic and Organic Chemicals
  - Metals
  - Other Trace Elements
  - Organic Compounds
- Other Chemical Parameters
  - pH
  - Dissolved Oxygen
  - Salinity
  - Organic Matter
  - Other
- Physical Parameters

Ecological Processes
- Energy Flow
  - Primary Production
  - Net Ecosystem Production
  - Growth Efficiency
- Material Flow
  - Organic Carbon Cycling
  - Nitrogen and Phosphorus Cycling
  - Other Nutrient Cycling

Hydrology and Geomorphology
- Surface and Groundwater flows
  - Pattern of Surface flows
  - Hydrodynamics
  - Pattern of Groundwater flows
  - Salinity Patterns
  - Water Storage
- Dynamic Structural Characteristics
  - Channel/Shoreline Morphology, Complexity
  - Extent/Distribution of Connected Floodplain
  - Aquatic Physical Habitat Complexity
- Sediment and Material Transport
  - Sediment Supply/Movement
  - Particle Size Distribution Patterns
  - Other Material Flux

Natural Disturbance Regimes
- Frequency
- Intensity
- Extent
- Duration

Source: Science Advisory Board (2002).

Deposition of Air Pollutants to the Great Waters, Third Report to Congress (U.S. Environmental Protection Agency, 2000b).

9.10.2.2 Ecosystem Exposures – Particle Deposition

Airborne particles, their precursors, and their transformation products are removed from the atmosphere by wet and dry deposition processes. This atmospheric cleansing process fortunately lowers the long-term buildup of lethal concentrations of these pollutants in the air and moderates the potential for direct human health effects caused by their inhalation. Unfortunately, these deposition processes also mediate the transfer of PM pollutants to other environmental media where they can and do alter the structure, function, diversity, and sustainability of complex ecosystems.

The potential effects of PM deposition on vegetation and ecosystems encompass the full range, scales, and properties of biological organization listed under Biotic Condition. Exposure to a given mass concentration of airborne PM, however, may lead to widely differing responses, depending on the particular mix of deposited particles**.** Particulate matter is not a single pollutant, but rather a heterogeneous mixture of particles differing in size, origin, and chemical composition. This heterogeneity exists across individual particles within samples from individual sites and, to an even greater extent, between samples from different sites. Thus far, atmospheric PM has been defined, for regulatory purposes, mainly by size fractions and less clearly so in terms of chemical nature, structure, or source. While size is related to the mode and magnitude of deposition to vegetated landscapes and may be a useful surrogate for chemical constitution, PM size classes do not necessarily have specific differential relevance for vegetation effects (Whitby, 1978; U.S. Environmental Protection Agency, 1996a); that is, both fine- and coarse-mode particles may affect plants. Much of the burden of sulfates, nitrates, ammonium salts, and hydrogen ions resides in the atmosphere either dissolved in fog water or as liquid or solid aerosols. Therefore, assessment of atmospheric PM deposition and effects on vegetation unavoidably include discussion of nitrates and sulfates and associated compounds involved in acidic and acidifying deposition. Other important issues relate to trace elements and heavy metals often found in ambient airborne PM.

9.10.2.3 Direct and Indirect Effects on Ecosystems

The deposition of PM onto vegetation and soil, depending on its chemical composition (acid/base, trace metal, or nutrients, e.g., nitrates or sulfates), can produce direct or indirect responses within an ecosystem. Direct effects are chiefly physical. The effects of toxic particles

are both chemical and physical. Direct ecosystem effects have been observed largely in the neighborhood of point sources such as limestone quarries; cement kilns; and iron and lead smelting factories. The nitrates and sulfates whose indirect effects occur through the soil environment are considered to be the stressors of greatest environmental significance. Upon entering the soil environment, they can alter the ecological processes of energy flow and nutrient cycling, inhibit nutrient uptake, change ecosystem structure, and affect ecosystem biodiversity. The soil environment is one of the most dynamic sites of biological interaction in nature. Bacterial communities are essential participants in the nitrogen and sulfur cycles that make these elements available for plant uptake. Fungi in association with plant roots form mycorrhizae, a mutualistic symbiotic relationship that is integral in mediating plant uptake of mineral nutrients. Changes in the soil environment that influence the role of the bacteria in nutrient cycling and fungi in nutrient uptake determine plant and ultimately ecosystem response..

Ecosystem response to pollutant deposition is a direct function of the level of sensitivity of the ecosystem and its ability to ameliorate resulting change. The Essential Ecological Attributes (EEA's) provide a hierarchical framework for determining ecosystem status associated wiht the last three EEA's (Table 9-14). The first three are considered to be "patterns" and the last three "processes". The ecological processes create and maintain the ecosystem elements in the patterns of the first three EEA's. The patterns in turn affect how the ecosystem processes are expressed. Patterns at the higher level of biological organization emerge from the interactions and selection processes at localized levels. Changes in patterns or processes result in changes in the status and functioning of an ecosystem. The relationships among the EEAs are complex because all are interrelated (i.e., changes in one EEA may affect, directly or indirectly, every other EEA). The functioning of the ecological processes associated with the Ecological Process EEAs must be scaled in both time and space and propagated to the more complex levels of community interaction to produce observable ecosystem changes.

Both ecosystem structure (Biotic condition) and functions (Ecological Processes) are important in providing products and services essential to human existence on planet Earth. Ecosystem processes maintain clean water, clean air, a vegetated earth, and a balance of organisms. Also included in the benefits are absorption and breakdown of pollutants, cycling of nutrients, binding of the soil, degradation of organic waste, maintenance of a balance of gases in the air, regulation of radiation balance, climate, and fixation of solar energy. Concern has arisen

in recent years regarding biodiversity and the integrity of ecosystems. Human-induced changes in biotic diversity and alterations in EEA patterns and the functioning of EEA processes are the two most dramatic ecological trends of the past century. Biodiversity is of major importance in the functioning of ecosystems.

Nitrogen in nature may be divided into two groups: nonreactive (N_2) and reactive (Nr). Although nitrogen as molecular nitrogen (N_2) is the most abundant element in the atmosphere, it is not available to more than 99% of living organisms. It only becomes available after it is converted into reactive (Nr) forms. Reactive Nr includes all biologically, photochemically, and radioactively active nitrogen compounds in the earth's atmosphere and biosphere. Among those included are: the inorganic reduced forms of nitrogen (e.g., ammonia [NH_3] and ammonium [NH_4^+]), inorganic oxidized forms (e.g., nitrogen oxide [NO_x], nitric acid [$HNO_{3]}$, nitrous oxide [N_2O], and nitrate [NO_3^-]) , and organic compounds (e.g., urea, amine, proteins, and nucleic acids)]).

The overall increase in global Nr is the result of three main causes: (1) widespread cultivation of legumes, rice and other crops that promote conversion of N_2 to organic nitrogen through biological nitrogen fixation; (2) combustion of fossil fuels, which converts both atmospheric N_2 and fossil nitrogen to reactive NO_x; and (3) the Haber-Bosch process, which converts nonreactive NH_3 to sustain food production and some industrial activities. The deposition of nitrogen in the United States from human activity has doubled between 1961 and 1997 due mainly to the use of inorganic nitrogen fertilizers and the emissions of nitrogen oxides (NO_x) from fossil fuel emissions with the largest increase occurring in the 1960s and 1970s. As a result, Nr is accumulating in various environmental reservoirs, e.g., the atmosphere, soils and waters. The accumulation of Nr in the terrestrial environment results in major changes in the nitrogen cycle, as it moves thru various environmental reservoirs depicted in Figure 9-24.

The results of increased Nr in the global system and the wide variety changes in the nitrogen cycle are both beneficial and detrimental to the health and welfare of humans and ecosystems. The synthetic fertilizers used in cultivation and the cultivation-induced bacterial nitrogen fertilization (BNF) sustain a large portion of the world's population.

Reactive nitrogen can be widely dispersed and accumulate in the environment when the rates of its formation exceed the rates of removal via denitrification. Nr creation and accumulation is projected to increase as per capita use of resources by human populations

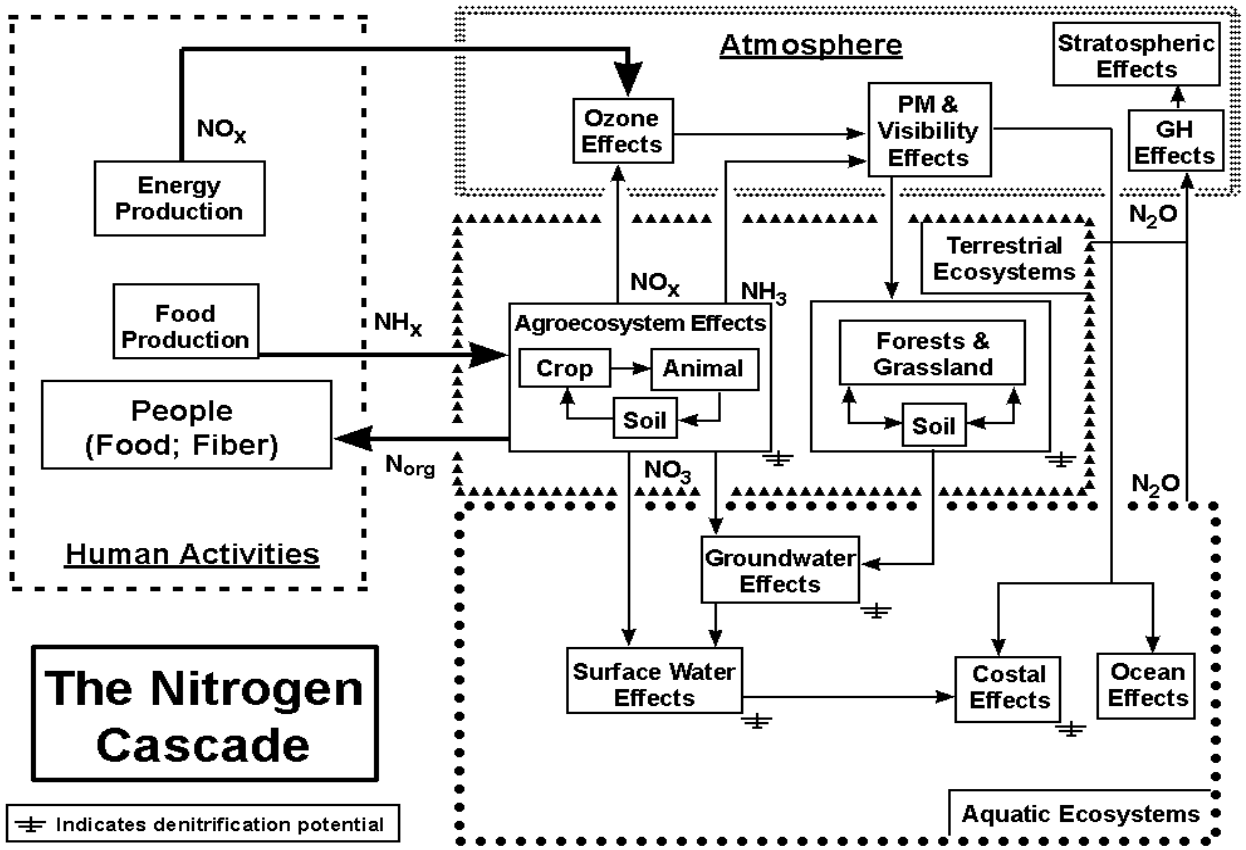

Figure 9-24. Illustration of the nitrogen cascade showing the movement of the human-produced reactive nitrogen (Nr) as it cycles through the various environmental reservoirs in the atmosphere, terrestrial ecosystems, and acquatic ecosystems.

Modified from Galloway and Cowling (2002).

increases. The cascade of environmental effects resulting from increases in Nr include the following: (1) production of tropospheric ozone and aerosols that induce human health and environmental problems; (2) increases in the productivity in forests and grasslands followed by decreases wherever deposition increases significantly and exceeds critical thresholds; Nr additions probably also decrease biodiversity in many natural habitats; (3) in association with sulfur is responsible for acidification and loss of biodiversity in lakes and streams in many regions of the world; (4) eutrophication, hypoxia, loss of biodiversity, and habitat degradation in coastal ecosystems. [Eutrophication is now considered the biggest pollution problem in coastal

waters.] (5) contributes to global climate change and stratospheric ozone depletion, which can in turn affect ecosystems and human health (Figure 9-24).

Direct effects of Nr on human health and the environment include (1) increased yields and nutritional quality of food needed to meet dietary requirements and food preferences for growing populations; (2) respiratory and cardiac disease induced by exposure to high ozone and fine PM concentrations; (3) decreased growth and yields of certain sensitive plant species; (4) nitrate and nitrite contamination of drinking water leading to the "blue baby syndrome" and certain types of cancer; and (5) blooms of toxic algae, with resultant injury to humans and to fish and other aquatic life.

Indirect effects on societal values include: (1) regional hazes that decrease visibility at scenic vistas and airports; (2) depletion of stratospheric ozone by N_2O emissions; (3) global climate change induced by emissions of N_2O and formation of tropospheric ozone; (4) formation of acidic deposition. The magnitude of Nr flux often determines whether effects are beneficial or detrimental (Table 9-15).

Among the most important effects of chronic nitrogen deposition are changes in the composition of plant communities, disruptions in nutrient cycling, increased emissions of nitrogenous greenhouse gases from soil and accumulation of nitrogen compounds resulting in the enhanced availability of nitrate or ammonium, the soil-mediated effects of acidification, and increased susceptibility to stress factors. A major concern is "nitrogen saturation," the result of the atmospheric deposition of large amounts of particulate nitrates, often as a consequence of slow deposition over long time periods. Nitrogen saturation results when additions to soil background nitrogen (nitrogen loading) exceeds the capacity of plants and soil microorganisms to utilize and retain nitrogen. Under these circumstances, disruptions of ecosystem functioning may result.

Although soils of most North American forest ecosystems are nitrogen limited, there are some that exhibit severe symptoms of nitrogen saturation. Increases in soil nitrogen play a selective role in ecosystems. Plant succession patterns and biodiversity are affected significantly by chronic nitrogen additions in some North American ecosystems. Plants adapted to living in an environment of low nitrogen availability will be replaced by nitrophilic plants capable of using increased nitrogen because they have a competitive advantage when nitrogen becomes more readily available. Long-term nitrogen fertilization studies in both New England and

TABLE 9-15. EFFECTS OF REACTIVE NITROGEN

Direct effects of Nr on ecosystems include:
• Increased productivity of Nr-limited natural ecosystems.
• Ozone-induced injury to crop, forest, and natural ecosystems and predisposition to attack by pathogens and insects.
• Acidification and eutrophication effects on forests, soils, and freshwater aquatic ecosystems.
• Eutrophication and hypoxia in coastal ecosystems.
• N saturation of soils in forests and other natural ecosystems.
• Biodiversity losses in terrestrial and aquatic ecosystems and invasions by N-loving weeds.
• Changes in abundance of beneficial soil organisms that alter ecosystem functions.
Indirect effects of Nr on other societal values include:
• Increased wealth and well being of human populations in many parts of the world.
• Significant changes in patterns of land use.
• Regional hazes that decrease visibility at scenic vistas and airports.
• Depletion of stratospheric ozone by N_2O emissions.
• Global climate change induced by emissions of N_2O and formation of tropospheric ozone.
• Damage to useful materials and cultural artifacts by ozone, other oxidants, and acid deposition.
• Long-distance transport of Nr which causes harmful effects in countries distant from emission sources and/or increased background concentrations of zone and fine particulate matter.
In addition to these effects, it is important to recognize that:
• The magnitude of Nr flux often determines whether effects are beneficial or detrimental.
• All of these effects are linked by biogeochemical circulation pathways of Nr.
• Nr is easily transformed among reduced and oxidized forms in many systems. Nr is easily distributed by hydrologic and atmospheric transport processes.

Europe suggest that some forests receiving chronic inputs of nitrogen may decline in productivity and experience greater mortality. Declining coniferous forest stands with slow nitrogen cycling may be replaced by deciduous fast-growing forests that cycle nitrogen more rapidly.

Linked to the nitrogen cascade (see Figure 9-24) is the deposition of Nr and sulfates and the associated hydrogen ion in acidic precipitation, a critical environmental stress that affects forest landscapes and aquatic ecosystems in North America, Europe, and Asia. Composed of ions, gases, and particles derived from gaseous emissions of sulfur dioxide (SO_2), nitrogen

oxides (NO_x), ammonia (NH_3) and particulate emissions of acidifying and neutralizing compounds, acidic precipitation is highly variable across time and space. Its deposition and the resulting soil acidity can lead to plant nutrient deficiencies and to high aluminum-to-nutrient ratios that limit plant uptake of calcium and magnesium and create a nutrient deficiency. Aluminum accumulation in root tissue can reduce calcium uptake and causes Ca^{2+}deficiencies. Tree species can be adversely affected if altered Ca/Al ratios impair calcium or magnesium uptake. Calcium is essential in the formation of wood and the maintenance of the primary plant tissues necessary for tree growth.

Notable impacts of excess nitrogen deposition also have been observed with regard to aquatic systems. For example, atmospheric nitrogen deposition into soils in watershed areas feeding into estuarine sound complexes (e.g., the Pamlico Sound of North Carolina) appear to contribute to excess nitrogen flows in runoff (especially during and after heavy rainfall events such as hurricanes) from agricultural practices or other uses (e.g., fertilization of lawns or gardens), massive influxes of such nitrogen into watersheds and sounds can lead to dramatic decreases in water oxygen and increases in algae blooms that can cause extensive fish kills and damage to commercial fish and sea food harvesting.

An important characteristic of fine particles is their ability to affect flux of solar radiation passing through the atmosphere directly, by scattering and absorbing solar radiation, and indirectly, by acting as cloud condensation nuclei that, in turn, influence the optical properties of clouds. Regional haze has been estimated to diminish surface solar visible radiation by approximately 8%. Crop yield have been reported as being sensitive to the amount of sunlight receive, and crop losses have been attributed to increased airborne particle levels in some areas of the world.

9.10.3 Visibility Effects of Airborne Particles

Visibility is defined as the degree to which the atmosphere is transparent to visible light and the clarity and color fidelity of the atmosphere. Visual range is the farthest distance a black object can be distinguished against the horizontal sky. Visibility impairment is any humanly perceptible change in visibility. For regulatory purposes, visibility impairment, characterized by light extinction, visual range, contrast, and coloration, is classified into two principal forms: (1) “reasonably attributable” impairment, attributable to a single source or small group of

sources, and (2) regional haze, any perceivable change in visibility caused by a combination of many sources over a wide geographical area.

Visibility is measured by human observation, light scattering by particles, the light extinction-coefficient, and parameters related to the light-extinction coefficient (visual range and deciview scale), and fine PM mass concentrations.

The air quality within a sight path will affect the illumination of the sight path by scattering or absorbing solar radiation before it reaches the Earth's surface. The rate of energy loss with distance from a beam of light is the light extinction coefficient. The light extinction coefficient is the sum of the coefficients for light absorption by gases (σ_{ag}), light scattering by gases (σ_{sg}), light absorption by particles (σ_{ap}), and light scattering by particles (σ_{sp}). Corresponding coefficients for light scattering and absorption by fine and coarse particles are σ_{sfp} and σ_{afp} and σ_{scp} and σ_{acp}, respectively. Visibility within a sight path longer than approximately 100 km (60 mi) is affected by the change in the optical properties of the atmosphere over the length of the sight path.

Visual range was developed for and continues to be used as an aid in military operations and to a lesser degree in transportation safety. Visual range is commonly taken to be the greatest distance a dark object can be seen against the background sky. The deciview is an index of haziness. A change of 1 or 2 deciviews is seen as a noticeable change in the appearance of a scene.

Under certain conditions, fine particle mass concentrations may be used as a visibility indicator. However, the relationship may differ between locations and for different times of the year. Also, measurement should be made under dry conditions.

Visibility impairment is associated with airborne particle properties, including size distributions (i.e., fine particles in the 0.1- to 1.0-µm size range) and aerosol chemical composition, and with relative humidity. With increasing relative humidity, the amount of moisture available for absorption by particles increases, thus causing the particles to increase in both size and volume. As the particles increase in size and volume, the light scattering potential of the particles also generally increases. Visibility impairment is greatest in the eastern United States and Southern California. In the eastern United States, visibility impairment is caused primarily by light scattering by sulfate aerosols and, to a lesser extent, by nitrate particles and organic aerosols, carbon soot, and crustal dust. Up to 86% of the haziness in the eastern United

States is caused by atmospheric sulfate. Further West, scattering contributions to visibility impairment decrease to from 25 to 50%. Light scattering by nitrate aerosols is the major cause of visibility impairment in southern California. Nitrates contribute about 45% to the total light extinction in the West and up to 17% of the total extinction in the East. Organic particles are the second largest contributors to light extinction in most U.S. areas. Organic carbon is the greatest cause of light extinction in the West, accounting for up to 40% of the total extinction and up to 18% of the visibility impairment in the East. Coarse mass and soil, primarily considered "natural extinction," is responsible for some of the visibility impairment in the West, accounting for up to 25% of the light extinction.

9.10.4 Materials Damage Related to Airborne Particulate Matter

Building materials (metals, stones, cements, and paints) undergo natural weathering processes from exposure to environmental elements (wind, moisture, temperature fluctuations, sun light, etc.). Metals form a protective film of oxidized metal (e.g., rust) that slows environmentally induced corrosion. On the other hand, the natural process of metal corrosion from exposure to natural environmental elements is enhanced by exposure to anthropogenic pollutants, in particular SO_2, that render the protective film less effective.

Dry deposition of SO_2 enhances the effects of environmental elements on calcereous stones (limestone, marble, and cement) by converting calcium carbonate (calcite) to calcium sulfate dihydrate (gypsum). The rate of deterioration is determined by the SO_2 concentration, the stone's permeability and moisture content, and the deposition rate; however, the extent of the damage to stones produced by the pollutant species apart from the natural weathering processes is uncertain. Sulfur dioxide also has been found to limit the life expectancy of paints by causing discoloration and loss of gloss and thickness of the paint film layer.

A significant detrimental effect of particle pollution is the soiling of painted surfaces and other building materials. Soiling changes the reflectance of an opaque material and reduces the transmission of light through transparent materials. Soiling is a degradation process that requires remediation by cleaning or washing, and, depending on the soiled surface, repainting. Available data on pollution exposure indicates that particles can result in increased cleaning frequency of the exposed surface and may reduce the usefulness of the soiled material. Attempts have been made to quantify the pollutants exposure levels at which materials damage and soiling have been

perceived. However, to date, insufficient data are available to advance our knowledge regarding perception thresholds with respect to pollutant concentration, particle size, and chemical composition.

9.10.5 Atmospheric Particle Effects on Global Warming Processes and Transmission of Solar Ultraviolet Radiation

The physical processes (i.e., scattering and absorption) responsible for airborne particle effects on transmission of solar visible and ultraviolet radiation are the same as those responsible for visibility degradation. Scattering of solar radiation back to space and absorption of solar radiation determine the effects of an aerosol layer on solar radiation.

Atmospheric particles greatly complicate projections of future trends in global warming processes because of emissions of greenhouse gases; consequent increases in global mean temperature; resulting changes in regional and local weather patterns; and mainly deleterious (but some beneficial) location-specific human health and environmental effects. The body of available evidence, ranging from satellite to in situ measurements of aerosol effects on radiation receipts and cloud properties, is strongly indicative of an important role in climate for aerosols. This role, however, is poorly quantified. No significant advances have been made in reducing the uncertainties assigned to forcing estimates provided by the IPCC for aerosol-related forcing, especially for black carbon-containing aerosol. The IPCC characterizes the scientific understanding of greenhouse gas-related forcing as "high" in contrast to that for aerosol, which it describes as "low" to "very low."

Quantification of the effect of anthropogenic aerosol on hydrological cycles requires more information than is presently available regarding ecosystems responses to reduced solar radiation and other changes occurring in the climate system. However, several global scale studies indicate that aerosol cooling alone can slow down the hydrological cycle, while cooling plus the nucleation of additional cloud droplets can dramatically reduce precipitation rates.

In addition to direct climate effects through the scattering and absorption of solar radiation, particles also exert indirect effects on climate by serving as cloud condensation nuclei, thus affecting the abundance and vertical distribution of clouds. The direct and indirect effects of particles appear to have significantly offset global warming effects caused by the buildup of greenhouse gases on a globally-averaged basis. However, because the lifetime of particles is much shorter than that required for complete mixing within the Northern Hemisphere, the

climate effects of particles generally are felt much less homogeneously than are the effects of long-lived greenhouse gases.

Any effort to model the impacts of local alterations in particle concentrations on projected global climate change or consequent local and regional weather patterns would be subject to considerable uncertainty.

Atmospheric particles also complicate estimation of potential future impacts on human health and the environment projected as possible to occur because of increased transmission of solar ultraviolet radiation (UV-B) through the Earth's atmosphere, secondary to stratospheric ozone depletion due to anthropogenic emissions of chlorofluorcarbons (CFCs), halons, and certain other gases. The transmission of solar UV-B radiation is affected strongly by atmospheric particles. Measured attenuations of UV-B under hazy conditions range up to 37% of the incoming solar radiation. Measurements relating variations in PM mass directly to UV-B transmission are lacking. Particles also can affect the rates of photochemical reactions occurring in the atmosphere, e.g., those involved in catalyzing tropospheric ozone formation. Depending on the amount of absorbing substances in the particles, photolysis rates either can be increased or decreased. Thus, atmospheric particle effects on UV-B radiation, which vary depending on size and composition of particles, can differ substantially over different geographic areas and from season to season over the same area. Any projection of effects of location-specific airborne PM alterations on increased atmospheric transmission of solar UV radiation (and associated potential human health or environmental effects) due to stratospheric ozone-depletion would, therefore, also be subject to considerable uncertainty.

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.

Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Ponce de Leon, A. (1999) Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch. Environ. Health 54: 398-411.

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.

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.

Bormann, F. H.; Likens, G. E. (1979) Catastrophic disturbance and the steady state in northern hardwood forests. Am. Sci. 67: 660-669.

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.; Goldberg, M. S. (2003) Size-fractionated particulate mass and daily mortality in eight Canadian cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 85-90. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (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.; 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: 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.

Chapin, F. S., III; Ruess, R. W. (2001) The roots of the matter. Nature (London) 411: 749, 751-752.

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.

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.

Dominici, F.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2002) Air pollution and mortality: estimating regional and national dose-response relationships. J. Am. Stat. Assoc. 97: 100-111.

Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S. L.; Samet, J. M. (2003) Shape of the exposure-response relation and mortality displacement in the NMMAPS database. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 91-96. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

Fairley, D. (2003) Mortality and air pollution for Santa Clara County, California, 1989-1996. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 97-106. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Fanucchi, M. V.; Wong, V. J.; Hinds, D.; Tarkington, B. K.; Van Winkle, L. S.; Evans, M. J.; Plopper, C. G. (2000) Repeated episodes of exposure to ozone alters postnatal development of distal conducting airways in infant rhesus monkeys. Am. J. Respir. Crit. Care Med. 161: A615.

Federal Register. (1971) National primary and secondary ambient air quality standards. F. R. (April 30) 36: 8186-8201.

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. (1996) National ambient air quality standards for particulate matter; proposed rule. F. R. (December 13) 61: 65,638-65,713.

Federal Register. (1997) National ambient air quality standards for particulate matter; final rule. F. R. (July 18) 62: 38,652-38,752.

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.

Galloway, J. N.; Cowling, E. B. (2002) Reactive nitrogen and the world: 200 years of change. Ambio 31: 64-71.

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.

Garner, J. H. B. (1994) Nitrogen oxides, plant metabolism, and forest ecosystem response. In: Alscher, R. G.; Wellburn, A. R., eds. Plant responses to the gaseous environment: molecular, metabolic and physiological aspects, [3rd international symposium on air pollutants and plant metabolism]; June 1992; Blacksburg, VA. London, United Kingdom: Chapman & Hall; pp. 301-314.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Gauderman, W. J.; Gilliland, G. F.; Vora, H.; Avol, E.; Stram, D.; McConnell, R.; Thomas, D.; Lurmann, F.; Margolis, H. G.; Rappaport, E. B.; Berhane, K.; Peters, J. M. (2002) Association between air pollution and lung function growth in southern California children: results from a second cohort. Am. J. Respir. Crit. Care Med. 166: 76-84.

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].

Guderian, R.; Tingey, D. T.; Rabe, R. (1985) Effects of photochemical oxidants on plants. In: Guderian, R., ed. Air pollution by photochemical oxidants: formation, transport, control, and effects on plants. Berlin, Federal Republic of Germany: Springer-Verlag; pp. 127-333. (Billings, W. D.; Golley, F.; Lange, O. L.; Olson, J. S.; Remmert, H., eds. Ecological studies: analysis and synthesis, v. 52).

Harwell, M. A.; Myers, V.; Young, T.; Bartuska, A.; Gassman, N.; Gentile, J. H.; Harwell, C. C.; Appelbaum, S.; Barko, J.; Causey, B.; Johnson, C.; McLean, A.; Smola, R.; Templet, P.; Tosini, S. (1999) A framework for an ecosystem integrity report card. BioScience 49: 543-556.

Health Effects Institute. (2002) Reanalysis of National Morbidity, Mortality, and Air Pollution Study (NMMAPS) [letter with attachments]. Boston, MA: May 30.

Health Effects Institute. (2003) Revised analyses of time-series studies of air pollution and health. Boston, MA: Health Effects Institute; special report.

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.

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.

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.

International Commission on Radiological Protection. (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, pp. 1-482).

Ito, K. (2003) Associations of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 143-156. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Ito, K.; Thurston, G. D. (1996) Daily PM_{10}/mortality associations: an investigation of at-risk subpopulations. J. Exposure Anal. Environ. Epidemiol. 6: 79-95.

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.

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.; 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.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM10 associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling–interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. (2003) Replication of reanalysis of Harvard Six-City mortality study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 165-172. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.
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).
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.
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.; 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.
Mäkelä, J. M.; Aalto, P.; Jokinen, V.; Pohja, T.; Nissinen, A.; Palmroth, S.; Markkanen, T.; Seitsonen, K.; Lihavainen, H.; Kulmala, M. (1997) Observations of ultrafine aerosol particle formation and growth in boreal forest. Geophys. Res. Lett. 24: 1219-1222.
Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.
Mar, T. F.; Norris, G. A.; Larson, T. V.; Wilson, W. E.; Koenig, J. Q. (2003) Air pollution and cardiovascular mortality in Phoenix, 1995-1997. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 177-182. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
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 diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.

Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.

Moolgavkar, S. H. (2003) Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 183-198. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

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) Risk assessment in the federal government: managing the process. Washington, DC: National Academy Press. Available: http://books.nap.edu/books/POD115/html/index.html (3 June 2003).

National Research Council. (1994) Science and judgment in risk assessment. Washington, DC: National Academy Press. Available: http://www.nap.edu/books/030904894X/html/ (4 June 2003).

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/books/0309073375/html/ (4 June 2003).

National Science and Technology Council. (1998) National acid precipitation assessment program biennial report to Congress: an integrated assessment; executive summary. Washington, DC: National Science and Technology Council, Committee on Environment and Natural Resources. Available: www.nnic.noaa.gov/CENR/NAPAP/NAPAP_96.htm [2003 June 25].

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.

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.

Odum, E. P. (1989) Ecology and our endangered life-support systems. Sunderland, MA: Sinauer Associates, Inc.; pp. 58-66, 108-118.

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.; 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.
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.; 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.
Peters, A.; Kotesovec, F.; Skorkovsky, J.; Brynda, J.; Heinrich, J. (1999c) 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, 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. (2003) Aspects of the spatial variability of PM2.5 concentrations within urban areas of the United States. J. Air Waste Manage. Assoc.: 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; 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 PM_{10} 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.; 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.
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.
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.
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.
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. (1993) Air pollution and daily mortality in Birmingham, Alabama. Am. J. Epidemiol. 137: 1136-1147.
Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.
Schwartz, J. (2000a) The distributed lag between air pollution and daily deaths. Epidemiology 11: 320-326.
Schwartz, J. (2000b) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151: 440-448.
Schwartz, J. (2003) Daily deaths associated with air pollution in six US cities and short-term mortality displacement in Boston. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 219-226. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.
Schwartz, J.; 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.
Science Advisory Board. (2002) A framework for assessing and reporting on ecological condition: an SAB report. Young, T. F.; Sanzone, S., eds. Washington, DC: U.S. Environmental Protection Agency, Ecological Processes and Effects Committee; report no. EPA-SAB-EPEC-02-009. Available at: http://www.epa.gov/science1/index.html (27 January 2003).
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. (2003) Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 227-230. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
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.
Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) Effect of outdoor airborne particulate matter on daily death counts. Environ. Health Perspect. 103: 490-497.
Thurston, G. D.; Ito, K.; 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. (2000a) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.
Tolbert, P. E.; Mulholland, J. A.; Maclntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.; Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000b) Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia. Am. J. Epidemiol. 151: 798-810.
Treshow, M. (1980) Pollution effects on plant distribution. Environ. Conserv. 7: 279-286.
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. Code. (1991) Clean Air Act, §108, air quality criteria and control techniques, §109, national ambient air quality standards. U. S. C. 42: §§7408-7409.
U.S. Court of Appeals for the District of Columbia. (2002) American Trucking Associations, Inc. vs. U.S. Environmental Protection Agency. 283 F.3d 355, 378-79 (D.C. Cir. 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) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-83/028aF-dF. 4v. Available from: NTIS, Springfield, VA; PB87-142378.

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) Deposition of air pollutants to the great waters. Third report to Congress. [Executive Summary]. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; report no. EPA-453/R-00-005.

U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; report no. EPA/600/8-90/057F. Available: http://cfpub.epa.gov/ncea/ [22 May, 2003].

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.

Wallace, L. A.; Emmerich, S. J.; Howard-Reed, C. (2002) Continuous measurements of air change rates in an occupied house for 1 year: the effect of temperature, wind, fans, and windows. J. Exposure Anal. Environ. Epidemiol. 12: 296-306.

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.

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

Wong, T. W.; Lau, T. S.; Yu, T. S.; Neller, A.; Wong, S. L.; Tam, W.; Pang, S. W. (1999) Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup. Environ. Med. 56: 679-683.

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.

Woodwell, G. M. (1970) Effects of pollution on the structure and physiology of ecosystems: changes in natural ecosystems caused by many different types of disturbances are similar and predictable. Science (Washington, DC) 168: 429-433.

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. (2003) Airborne particles and hospital admissions for heart and lung disease. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 241-248. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

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.

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.

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 (±CI) Only PM in Model	RR (±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 (±11.7)
Boston, MA	1.06 (1.04, 1.09)	—	24 (±12.8)
Topeka, KS	0.98 (0.90, 1.05)	—	27 (±16.1)
St. Louis, MO	1.03 (1.00, 1.05)	—	31 (±16.2)
Kingston/Knoxville, TN	1.05 (1.00, 1.09)	—	32 (±14.5)
Steubenville, OH	1.05 (1.00, 1.08)	—	46 (±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)			
Respiratory Disease			
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)
COPD			
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 (±CI) Only PM in Model	RR (±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 90 percentile (10, 90). NR = not (±SD), 10 and 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 (±CI) per 25 μg/m³ PM Increase	Reported PM Levels Mean (Min/Max)[†]
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)
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/m³)	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] (Cough)	$PM_{2.5}$	1.19 (1.01, 1.42)[**]	18.0 (7.2, 37)[***]
	$PM_{2.5}$ 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] (Lower Resp. Symp.)	$PM_{2.5}$	1.44 (1.15-1.82)[**]	18.0 (7.2, 37)[***]
	$PM_{2.5}$ 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 μg/m³)	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 (±SD), 10 and 90 percentile (10,90) or R = range of values from min-max, no mean value reported.
[*]Change per 100 nmoles/m³
[**]Change per 20 μg/m³ for $PM_{2.5}$; per 5 μg/m³ for $PM_{2.5}$ sulfur; per 25 nmoles/m³ 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, -.0.51) 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.; 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.